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Allergic or Pseudo-Allergic Gastrointestinal Disorders

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Editorial

Intestinal complaints are frequent both in children and in adults. A direct link between food ingestion and subsequent gastrointestinal (GI) symptoms (such as pain, bloating, diarrhea, or constipation) is often suspected and easily categorized as adverse food reaction. And most often without asking for medical advice, patients experiment with food avoidance or specific restriction diets to relief their symptoms. These restriction diets become more and more fashionable and are easily promoted as a healthy lifestyle. After lactose-free diet, cow's milk protein-free diet and, more recently, gluten-free diet became very trendy. It is suspected that in the USA, a strict gluten-free diet is followed by significantly more individuals in form of self-medication for presumably gluten-related symptoms without seeking medical advice than by patients with well-diagnosed celiac disease. A rising market for lactose-free and now gluten-free products parallels this trend – often promoted with the notion of healthier and better food. A recent analysis [1] showed that commercially available foods for children with a claim such as being gluten-free are not necessarily of high nutritional quality. In addition, the notion of a healthier life by using restriction diets is not necessarily true, especially for children, who are potentially exposed to nutritional deficiencies. Without any diagnostic analyses, often in self-evaluation, patients report on intolerance or "allergic" reactions to a specific food or food class. In the present series of 4 articles, we address this issue, raising the question of a link between food components and adverse reactions as true allergic reactions or mechanisms of food-induced intestinal complaints other than allergy, calling them "pseudo-allergic gastrointestinal disorders." Over the last two decades, there was a marked increase of new allergic and pseudo-allergic GI conditions, either due to a better recognition of these diseases or a true increase of their incidence, or a combination of both, which is the most likely explanation.

The terms food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctitis (FPIAP) describe a well-defined but less well-known form of cow's milk allergy in infants and children. In contrast to classical cow's milk or other food allergies, FPIES/FPIAP is a non-IgE-mediated syndrome. In his update on FPIES, Professor Dupont [2] describes two main clinical presentations: a chronic form characterized by recurrent vomiting in patients repeatedly exposed to the offending food, and an acute form occurring after a single ingestion of the offending food within 1–4 h with massive vomiting, often followed by (bloody) diarrhea. In rare cases, FPIES can lead to severe dehydration, lethargy, and a hypovolemic shock responding to intravenous fluids but not to catecholamines. In contrast to other forms of cow's milk allergy, no skin or extraintestinal symptoms occur. In infants, FPIES is most frequently caused by cow's milk protein, followed by soy. In older children or adults, FPIES may occur to solid foods (grains like rice, oat, meats, fish, egg, and vegetables). Occasionally, FPIES occurs in the newborn or in exclusively breastfed infants, caused by the mother's consumption of offending foods. FPIAP is a common cause of rectal bleeding in the breastfed neonate.

A different and probably pseudo-allergic, but inflammatory, GI disorder also caused by cow's milk is in the form of an eosinophilic GI disorder (EGID). EGID can occur in patients with well-known allergy as well as in patients without any notion of atopy or allergy. The present

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review of Doctor Koutri and Professor Papadopoulou [3] highlights that the clinical presentation depends on the involved GI sites as well as on the extent and the depth of eosinophilic inflammation of the intestinal mucosa, submucosa, or muscularis. Eosinophilic esophagitis can occur at any age presenting as unspecific feeding disorder in infants and young children followed by vomiting and abdominal pain in older children, while adolescents and adults often experience dysphagia and food impaction. Patients with eosinophilic gastritis or gastroenteritis present with abdominal pain, nausea, vomiting, early satiety, sometimes associated with failure to thrive or weight loss. Patients with diffuse small intestinal involvement may develop malabsorption, anemia, and hypoalbuminemia. Involvement of the colon leads most often to abdominal pain and (bloody) diarrhea. As for FPIES or FPAP, cow's milk proteins are the most frequent triggers, but EGID caused by wheat, soy, or eggs were also reported.

Intolerance of the milk sugar lactose makes the clinical picture even more complex. Very often patients and parents confound cow's milk protein allergy and intolerance of lactose, considerably complicating the clinical care for these patients. Professors Berni-Canani and Di Costanzo [4] review the recent knowledge on lactose intolerance, a truly nonallergic but still cow's milk-mediated GI disorder. The clinical presentation is dominated by abdominal pain, meteorism, and watery diarrhea. Since primary lactase deficiency is genetically determined, and approximately 70% of the global adult population is lactase nonpersistent (hypolactasia), the majority of individuals do not tolerate dairy containing high levels of lactose, while other milk products with lower lactose content or fermented milk products cause no symptoms.

The complexity of these intestinal symptoms and presumably allergic and nonallergic adverse food reactions is caused by the fact that different components of the same food can trigger different reactions. As shown for milk, the protein components elicit predominantly immune-mediated reactions, while carbohydrates provoke the vast majority of nonimmune-mediated symptoms. In addition, different foods or nutrients can provoke similar or identical GI symptoms, as introduced by discussing the recently described non-celiac gluten sensitivity (NCGS) syndrome [5]. This entity can provoke clinical symptoms resembling celiac disease or wheat allergy but also FPIES or EGID, indicating the need for specific diagnostic tests. In contrast to lactose intolerance or IgE-mediated food allergies, in patients suffering from FPIES, EGID, or NCGS, no specific diagnostic biomarker exists. And as discussed in this series of 4 articles [2–5], the suspected diagnosis of a food-induced adverse event has to be proven by a provocation test in a blinded fashion. If positive, an exclusion diet of the responsible antigen or food component is the most efficient treatment option, in addition to anti-inflammatory drugs if a patient is suffering from an eosinophilic GI disorder. Since the long-term outcome is different according to the underlying disease, a clear diagnosis is important to avoid exposing patients/individuals to an unnecessary or prolonged restriction diet. On the other hand, it is easily conceivable that depending on a variety of environmental factors the intestinal mucosa can react to food components in many ways causing specific adverse reactions. The recognition of inflammatory GI disorders, such as eosinophil GI diseases or allergic disorders including FPIES/FPIAP, as well as complex functional disorders, such as NCGS, is steadily increasing, allowing better diagnosing and treating patients. In addition, the incidence of all these GI diseases is steadily increasing without any clear explication. Some data indicate that the quality of food is quite different in 2018 compared to the 1980s or 1950s. Another interesting field of research is to learn to what extend the intestinal fecal microbiome can cause/modulate these adverse food reactions. The global rise of allergic and pseudo-allergic GI disorders parallels a strong demand in the global population for healthier food and avoidance strategies of certain food compounds accused of causing GI and extraintestinal symptoms and complaints.

Frank M. Ruemmele

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FOCUS

Food allergy in the form of syndromes, among which FPIES and FPIAP are gaining increased recognition

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Food Protein-Induced Enterocolitis Syndrome and Proctocolitis

by Christophe Dupont

Key insights

Food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP) are non-IgE-mediated, cellular allergic reactions to foods that account for around 40% of the cases of cow's milk allergy in infants and young children. FPIES manifests as either chronic or acute disease characterized by vomiting and diarrhea. In its acute form, FPIES can be life-threatening due to the ensuing dehydration. FPIAP typically occurs in the first few months of life as rectal bleeding in otherwise healthy infants who are either breastfed or formula-fed. The disease usually develops later in breastfed infants and has less severe histologic features compared to that occurring in formula-fed infants. Although FPIAP is transient, it represents one of the major causes of colitis during infancy.

Current knowledge

The chronic form of FPIES is related to permanent consumption of the offending food. Symptoms include intermittent emesis and chronic diarrhea, which may or may not correlate with the timing of food ingestion. The acute form of FPIES manifests as severe vomiting and diarrhea that occur upon exposure to the offending food following a period of avoidance. Adults experience the acute form of FPIES. Responsible foods include cow's milk, soy, fish, and shellfish. The majority of patients react to a single food item, although some have multiple food triggers. Family history of atopy is also found in 40–80% of patients with FPIES. FPIAP frequently occurs in breastfed infants where it is usually caused by cow's milk, soy, egg, and corn proteins. In formula-fed infants, FPIAP is typically caused by cow's milk and soy proteins.

Practical implications

Oral food challenge is often used to aid in diagnosis and to identify the dietary triggers. For both FPIES and FPIAP, avoidance of the offending food item(s) is the cornerstone of treatment. In patients with severe acute reactions, first-line treatment consists of rapid intravenous hydration using a 20 mL/kg normal saline bolus. Intravenous steroids may also be used to reduce intestinal inflammation and ondansetron is effective for halting emesis. For infants with FPIAP, the prognosis is usually good, with the majority of cases resolving in the first year of life. Treatment relies mainly on elimination of cow's milk, either in the mother's diet or in the infant's formula.

Syndrome	Treatment
FPIES	
Chronic	• Oral food challenge to identify the triggers • Avoidance of the offending food item(s), particularly cow's milk and soy
Acute	• Maintain hydration (oral or intravenous) • Ondansetron • Methylprednisolone • Monitor and correct acid-base and electrolyte abnormalities, methemoglobinemia • Constant monitoring of the patient
FPIAP	
Breastfed infants	• Maternal dietary restriction (milk and dairy products) • If the above is not effective, eliminate wheat and egg
Formula-fed infants	• Eliminate cow's milk and soy; use cow's milk extensive hydrolysate • Persistent bleeding may signify the need for amino acid formula

Summary of the treatment strategies for food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP).

Recommended reading

Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary (Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology). J Allergy Clin Immunol. 2017;139:1111–26.

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Allergic or Pseudo-Allergic Gastrointestinal Disorders

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Food Protein-Induced Enterocolitis Syndrome and Proctocolitis

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Key Messages

- **Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated syndrome of food allergy in infancy.**
- **FPIES puts the child at risk of severe vomiting and dehydration, responding to intravenous fluids and not to adrenalin.**
- **Food protein-induced allergic proctocolitis is a common cause of rectal bleeding in the breastfed neonate.**

Keywords
Food allergy · Non-IgE-mediated allergic reactions · Milk · Soy · Enterocolitis · Proctocolitis

Abstract
Non-IgE-mediated, also labeled cell-mediated, allergic reactions to foods are more common than usually thought and probably account for approximately more than 40% of cases of cow's milk allergy during infancy and young childhood. Food allergy is now described in the form of syndromes, among which food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP) are gaining increased recognition. FPIES occurs in infancy but may also occur in older children and in adults. The dominant symptom is emesis, repetitive in the chronic FPIES form and explosive in the acute form. Acute FPIES begins 1–4 h following ingestion of the offending food. Diarrhea is frequent, between 5 and 10 h later, and may be accompanied by lethargy and dehydration, which both characterize severity. Cow's milk is the most frequent food trigger, followed by soy. FPIES may develop up to 1 year of age, but may also occur in the newborn, and is possible in exclusively breastfed infants, in relation with the mother's consumption of offending foods. FPIES may occur to solid foods (grains like rice or oat, meats, fish, egg, and vegetables). When starting during infancy, FPIES has a good prognosis and disappears grossly at 2 years of age. FPIES to fish or shellfish is more frequent in older children and adults and is long lasting. International consensus guidelines for the diagnosis and management of FPIES have been published recently. FPIAP starts in the first few months of life and is typically manifested with rectal bleeding in well-appearing breastfed infants during the first months of life in reaction to cow's milk consumed by the mother. The condition is transient but represents one of the major causes of colitis during infancy.

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Food Protein-Induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) is a disease of infancy which may also occur in older children and in adults. The dominant symptom is emesis which appears repetitive in the chronic form of FPIES and explosive in the acute form. Acute FPIES begins 1–4 h following ingestion of the offending food, is followed by diarrhea, between 5 and 10 h later, and may be accompanied by lethargy and dehydration, which characterize severity [1]. There are neither respiratory nor skin manifestations. Cow's milk is one of the most frequent food triggers, followed by soy. The syndrome may develop up to 1 year of age but may also occur in the newborn. FPIES to cow's milk or soy is possible in exclusively breastfed infants, in relation with the mother's consumption of offending foods. Delayed-onset FPIES is usually a consequence from delayed introduction of cow's milk, soy, or solid foods, especially in breastfed infants. FPIES may occur to solid foods (grains like rice or oat, meats, fish, egg, and vegetables). When starting during infancy, FPIES has a good prognosis and disappears grossly at 2 years of age. FPIES to fish or shellfish is more frequent in older children and adults and is long lasting. International consensus guidelines for the diagnosis and management of FPIES have been published recently [2].

When starting during infancy, FPIES has a good prognosis and disappears grossly at 2 years of age

Clinical Presentation of FPIES

FPIES may appear either early in infants younger than 9 months or later. It may be mild-moderate or severe, and also classic, with no detectable food-specific IgE, or atypical when food-specific IgE are present [2].

The following description explains the chronic form of FPIES, when the offending food is consumed regularly, typically during infancy, and the acute form, usually associated with the accidental ingestion of the offending food, typically during an elimination diet. The acute form is also seen in older children or adults, when the offending food is not a staple food and is consumed only occasionally.

Chronic Form

In infants, the first period of the disease is marked by the chronic form, related with the permanent consumption of the offending food, typically cow's milk proteins at this age. It usually resolves within 3–10 days of elimination diet, mainly with a hypoallergenic formula in infants with milk FPIES [3]. In severe cases, FPIES starts in the first days of life in infants fed cow's milk- or soy-based formula. Intermittent emesis and chronic, sometimes bloody, diarrhea occurs without a specific temporal relationship with ingestion of the offending food [3–5]. Many associated symptoms may occur, such as abdominal distension, dehydration, weight loss, and lethargy. Biology may show anemia, elevated white blood count with eosinophilia, and hypoalbuminemia and metabolic acidosis. Abdominal radiographs may show intramural gas, suggesting necrotizing enterocolitis, and/or leading to anti-biotherapy following sepsis evaluation [6, 7]. FPIES may also manifest as acidemia and transient methemoglobinemia, especially in young infants with severe reactions, with some requiring a treatment, methylene blue and bicarbonate, according to cases [8].

Acute Form (Infancy)

Following a period of avoidance, the accidental or deliberate (during a food challenge) exposition to food (cow's milk proteins, egg) induces acute symptoms. These occur within 1–4 h, mainly in the form of emesis, usually projectile and repetitive, sometimes up to more than 10 times. In the meantime, the child appears pale and lethargic. Diarrhea occurs in infants and in severe reactions and starts later on, from 5 to 10 h after food ingestion, sometimes bloody and containing mucous. A stool sample would evidence the presence of leukocytes, eosinophils, and increased carbohydrate [3]. In extreme cases, abdominal distension is severe enough to suggest ileus, wrongly leading to an exploratory laparotomy [9]. In contrast, diarrhea may lack in less severe acute reactions, for example during a food challenge (when a limited amount of offending food is given) as well as in older children [10] or adults, in whom emesis dominates. Hypotension is possible and may lead to hypovolemic shock [11, 12]. Blood samples during positive food challenges show increased blood neutrophil counts, with a peak at 6 h [3].

Acute Form (Adults)

In adults, FPIES always appears in the acute form, with a syndrome similar to the acute form in infants, with severe nausea, abdominal cramps, protracted vomiting, and diarrhea [11]. Responsible foods are mainly mollusks (scallop), crustacean shellfish, and fish.

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Epidemiology and Responsible Foods

Few data relate to the epidemiology of FPIES. FPIES to cow's milk was reported in 0.34% of infants under the age of 12 months in Israel [13]. In Australian children aged less than 24 months, the incidence of FPIES was 15.4/100,000/year [14].

Among delayed gastrointestinal immune reactions to cow's milk, those with FPIES are considered to represent up to 40% in infants and young children with cow's milk allergy. [15]. In a large American referral population [16], the most common foods identified were milk (67%), soy (41%), rice (19%), oat (16%), and egg (11%). However, in the Australian study [14], the most common FPIES trigger was rice (45%), followed by cow's milk (33%) and egg (12%). In a retrospective Italian study (2004–2010), cow's milk was the most common trigger food (65%), followed by fish, egg, rice, soy, corn, poultry, and goat's milk [17]. FPIES may occur, rarely, in breastfed infants [18].

FPIES may occur, rarely, in breastfed infants

Most of the time (60%), patients react to a single food [16, 10], mainly cow's milk and soy, with 40% of infants potentially reacting to both. Solid foods may also induce FPIES (rice, oat, barley, chicken, turkey, egg white, green pea, and peanut) [1]. Solid-food FPIES tends to start later than cow's milk and soy FPIES, perhaps because solids are introduced later at around 6 months of age [10]. In an Italian study, the chief peculiarities of acute fish and shellfish FPIES [19], compared to more frequent cow's milk or soy FPIES, were an older age of onset, longer persistence, possibility of tolerating fish other than the offending fish, and adverse reactions to shellfish.

Multiple FPIES is more common than usually thought. In the Italian study [17], 85% of children reacted to a single food. In the Australian study [14], 20% had 2 food triggers and 12% had ≥3 food triggers. Infants with FPIES to multiple versus single food groups were younger at the initial episode (4.6 vs. 5.8 months) and more frequently had FPIES to fruits, vegetables, or both (66% vs. 21%). Sixty-four percent of infants with FPIES to multiple foods, which included cow's milk, had co-associated FPIES to solid foods. Infants with FPIES to fish reacted to other food groups in 42% of cases.

A family history of atopy is found in 40–80% of patients, with a positive food allergy family history in 20% of the cases [7]. Atopic diseases may develop later in life in infants with FPIES, eczema (23–57%), asthma or rhinitis (20%), or drug hypersensitivity [7]. Importantly, IgE positivity to other foods may reach 40% [10, 16], suggesting a role for these antibodies in the pathophysiology of the disease, at least in some cases.

Pathophysiology

The mechanisms underlying FPIES remain poorly characterized [20, 21]. During acute FPIES, blood testing will reveal an elevated white blood cell count with neutrophilia and thrombocytosis. If the syndrome is severe, the patient may also exhibit metabolic acidosis and methemoglobinemia. Increased serum cortisol levels have been described on oral food challenge (OFC) in infants with FPIES [22]. Stools may be positive for leukocytes, eosinophils, and increased carbohydrate content.

When diagnostic criteria were not available, endoscopy was carried out in symptomatic infants with cow's milk and/or soy FPIES, showing rectal ulceration and bleeding with friable mucosa [4]. When infants had FPIES manifested by chronic diarrhea, rectal bleeding, and/or failure to thrive, the main findings in radiographs were excess luminal fluid with air fluid levels, all signs which disappeared during appropriate elimination diet.

Natural History

Except for FPIES to fish and shellfish reported in older children and adults, FPIES develops during infancy and not beyond 1 year of age, suggesting a "window of physiologic susceptibility" [20, 23, 24].

FPIES is a condition which appears self-limiting and resolves without long-lasting sequelae [20]. Studies have been carried out in different countries and show great variations [25]. In Israel, cow's milk FPIES resolved by 3 years of age in 90% of cases [13]. In Korea, resolution was observed by 2 years of age and for soy FPIES by 14 months of age [26]. In the Italian study, 48% achieved tolerance at a mean age of 29 months, and the age of achieved tolerance for cow's milk was significantly lower compared to that of other foods (24 ± 8 vs. 53 ± 17 months) [17]. In the United States study, resolution of FPIES exhibited lower rates: 35% by 2 years of age, 70% by 3 years, and 85% by 5 years [16]. In Japanese patients with FPIES caused by cow's milk, the rate of tolerance acquisition was 18.8, 56.3, 87.5, and 96.9% at the ages of 6, 12, 24, and 36 months, respectively [27].

Solid FPIES resolves later, and grossly 50% of children outgrow rice or oat FPIES by 4–5 years of age [10, 16, 25]. The potential resolution of FPIES to seafood in older children and adults is unknown.

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Table 1. FPIES: diagnostic criteria (adapted from [2])

Chronic FPIES	
Milder presentation: Offending food is consumed at low doses (e.g., food allergens in breast milk), the child has intermittent vomiting and/or diarrhea, and poor weight gain, without dehydration or metabolic acidosis	Severe presentation: The offending food is ingested regularly (e.g., milk proteins in infant formula) and the child suffers constant vomiting and diarrhea, occasionally with blood, sometimes with dehydration and metabolic acidosis
For the diagnosis of chronic FPIES, symptoms resolve within days following elimination of the offending food(s) with acute recurrence when the food is reintroduced (vomiting within 1–4 h, diarrhea usually within 24 h)	
Acute FPIES	
Major criterion: Vomiting in the 1–4 h period after ingestion of the suspect food, without the "classic" IgE-mediated allergic skin or respiratory symptoms	Minor criteria: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1–4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency room visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5–10 h) 8. Hypotension 9. Hypothermia
According to Nowak-Węgrzyn et al. [2], the diagnosis of FPIES requires the major criterion and at least 3 minor criteria	

Diagnosis of FPIES

History-taking is key for the diagnosis of FPIES, analyzing the clinical features, excluding other etiologies, and preparing the food challenge [28].

Very frequently, FPIES is not recognized at the first visit, whether in its chronic or acute form; owing to both the lack of associated typical cutaneous and respiratory allergic symptoms [28] and the lack of knowledge of this "emerging" syndrome among physicians [29–32]. This lack of knowledge includes the common belief that rice, oat, and vegetables are hypoallergenic and can never induce an allergic reaction.

Such as for many situations in food allergy, the standard for diagnosing FPIES is the OFC. It is not mandatory when the clinical history shows repeated, frequently severe, reactions which disappear completely when the suspected food has been eliminated. Most of the time, OFCs are performed in order to check whether FPIES resolved and if the offending food may be reintroduced.

There is no biological test for FPIES such as for non-IgE-mediated gastrointestinal food allergies [33]. The presence of cow's milk-specific IgE has been described in one-third of patients with milk FPIES [34], a figure that seems higher in Japan [35]. In patients with food-specific IgE antibodies after the diagnosis of FPIES or during the course of the disease, the latter appeared to be more protracted [18, 36]. Measurement of serum food-specific IgE levels thus seems useful to identify patients at risk for persistent FPIES. Skin prick tests will be negative.

The atopy patch test has been tested in several studies of FPIES, with conflicting results [16, 37, 38], thus it is not recommended in routine practice.

Diagnostic criteria that have been published are indicated in Table 1. Differential diagnosis is presented in Table 2.

Management of FPIES

Food avoidance is the mainstay of treatment, with specific guidance for the treatment of accidental reactions and periodic reevaluations for tolerance, based mainly on OFC.

Avoidance

The elimination diet is similar to that done in food allergy. Cow's milk and soy FPIES are the most frequent and require an appropriate feeding. Breastmilk is the best, as usual. Formula feeding relies mainly on extensively hydrolyzed milk protein formula or on amino-acid formulas, which are requested by one half of patients with milk FPIES [39]. In case of chronic cow's milk and/or soy FPIES, symptoms resolve rapidly, within 1 week, often within 3 days of starting the elimination diet. Tube feed-

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Table 2. More common differential diagnosis of FPIES (adapted from [2])

Chronic FPIES	
Gastrointestinal reflux disease	Frequent situation, with chronic emesis, not leading to dehydration even if severe, may be related to milk allergy even in the absence of FPIES
Food protein-induced enteropathy	Chronic symptoms not temporarily associated with specific food intake, diarrhea, and failure to thrive, most commonly implicated foods are cow's milk, soy, wheat, and egg white; no recent publications on that entity
Eosinophilic gastroenteropathies (e.g., eosinophilic esophagitis, eosinophilic gastroenteritis)	Not associated with specific food intake, at least at a young age, chronic symptoms, vomiting less severe, positive IgE tests more likely; requires endoscopy
Celiac disease	Progressive malabsorption and abdominal distension, no temporal relationship with gluten intake positive
Lactose intolerance	In older children only, gas, bloating, cramps, diarrhea, borborygmi, and vomiting following ingestion of lactose (liquid milk, large doses of dairy products)
Hirschsprung's disease (neonatal period)	Marked abdominal distention, constipation, following delay in passage of the first meconium
Inborn errors of metabolism (neonatal period)	Neurologic manifestations, organomegaly, developmental delay, reaction to fruits
Acute FPIES	
Anaphylaxis	Symptoms begin within minutes to 2 h of exposure, positive IgE testing, other manifestations of anaphylaxis (rhinitis, pruritus, urticarial, etc.)
Infectious (viral, bacterial) gastroenteritis	Single episode of illness, fever, seasonal outburst
Sepsis, including meningitis (neonatal period)	May require infectious testing
Necrotizing enterocolitis (neonatal period)	Occurs only in the premature baby

ing or intravenous fluids may sometimes seem necessary at the beginning of treatment.

Oral Food Challenges

OFCs appear necessary, whether it is to establish the diagnosis of FPIES or to check the spontaneous evolution of the disease FPIES. The current recommendation is to challenge children every 18–24 months in patients without recent reactions. The exact timing of these OFCs to determine resolution has not been extensively investigated. The common attitude is an OFC within 12–18 months following the most recent reaction [23]. In Korea, a prospective study suggested earlier rechallenging: cow's milk FPIES resolved in all patients by the age of 2 years and soy FPIES by the age of 14 months [26]. In Israel, cow's milk FPIES was diagnosed in all children with milk by the age of 6 months, 50% resolved within the first year of life, 89% by the age of 2 years, and 90% by the age of 3 years [13].

Physician supervision for these OFCs is mandatory. A placement of a secure peripheral venous line is advisable in patients with previous severe reactions and in infants or older patients with anticipated difficult intravenous access: intravenous fluids and/or steroids are the most frequently used [17].

Treatment of Acute Reaction: A Need for Anticipation

Guidelines for the treatment of acute FPIES have been recently published [2] and are summarized in Table 3.

The first-line therapy for severe acute reactions, whether they occur accidently or during an OFC, is rapid intravenous hydration, using 20 mL/kg normal saline bolus. The role of intravenous access during OFCs has been studied [40].

Intravenous steroids may be used in case of severe reactions, likely to reduce intestinal inflammation. Epi-

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Table 3. Management of an acute FPIES episode at the medical facility (adapted from [2])

1	Attempt oral rehydration (e.g., breastfeeding or clear fluids)
2	If age 6 months and older: consider intramuscular ondansetron 0.15 mg/kg/dose (maximum 16 mg/dose)
3	Consider placing a peripheral intravenous line for normal saline bolus 20 mL/kg, repeat as needed
4	If placement of intravenous line is delayed due to difficult access and age is 6 months or older, administer intramuscular ondansetron 0.15 mg/kg/dose (maximum 16 mg/dose)
5	Consider administering intravenous methylprednisolone 1 mg/kg (maximum 60–80 mg/dose)
6	Monitor and correct acid base and electrolyte abnormalities
7	Correct methemoglobinemia if present
8	Monitor for resolution about 4–6 h from the onset of a reaction
9	Discharge after 4–6 h from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids
10	Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, respiratory distress

Different steps have to be taken according to the severity of the disease. In mild forms, emesis is limited to 1–2 episodes, in moderate forms >3 episodes of emesis are accompanied by mild lethargy, and in severe forms with >3 episodes of emesis and severe, the clinical pattern is marked by hypotonia, ashen or cyanotic appearance. Constant monitoring of the patient is mandatory during the whole treatment.

nephrine is not the primary treatment but may be used following rehydration in case of severe hypotension and cardiovascular shock. Epinephrine does not improve emesis and lethargy, the latter responding much more to intravenous fluid administration.

Intravenous ondansetron seems effective for stopping emesis during an OFC for FPIES [41]. Ondansetron was given at a dosage of 0.2 mg/kg per dose together with intravenous physiologic saline bolus in 5 children above 3 years of age with emesis during OFC: emesis and lethargy resolved within 10–15 min in 4 children treated with intravenous ondansetron and 1 child required an additional dose of ondansetron. In another child, ondansetron was given orally, and severe abdominal pain improved only with an additional intravenous ondansetron dose. In a small case series in young children, intramuscular ondansetron was effective to manage acute FPIES during OFC carried out in the physician's office [42].

All patients with FPIES need to be equipped with an emergency treatment plan, detailing the clinical features and the management of acute reactions. In case of a mild reaction, careful oral rehydration may be performed at home, whereas in case of a severe reaction, resuscitation necessitates the emergency department or inpatient unit.

Summary for FPIES

FPIES is gaining more and more interest and recognition, with its frequency potentially increasing. The syndrome is dangerous in its acute form and its recognition by health care professionals should be encouraged. The pathophysiology is still missing and its occurrence in both infants and adults remains unexplained. Guidelines now considerably help standardizing the treatment and providing families a guide to handle this very specific form of food allergy.

Food Protein-Induced Allergic Proctocolitis

Food protein-induced allergic proctocolitis (FPIAP) starts in the first few months of life. It was first described by Lake et al. [43] in 1982 in 6 breastfed infants with rectal bleeding that appeared during the first month of life. Well-appearing infants have blood-streaked stools, indicating a benign and transient condition, but probably one of the major causes of colitis during infancy [44–46].

Clinical Features

FPIAP frequently occurs in breastfed infants where it is usually caused by cow's milk, soy, egg, and corn pro-

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Table 4. Differential diagnosis of FPIAP (adapted from [1])

Severe FPIAP
Necrotizing enterocolitis
Sepsis
Intussusception
Volvulus
Hirschsprung's disease
FPIES
Mild/moderate FPIAP
Anal fissure
Perianal dermatitis/excoriations
Gastrointestinal infection (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* sp., parasites)
Coagulation disorders
Vitamin K deficiency

teins, whereas in formula-fed infants, FPIAP is typically caused by cow's milk and soy proteins.

The disease usually presents within the first 6 months of life, usually within the first month with normal to moderately loose stools and intermittent blood streaks. The onset is usually insidious, and a more or less prolonged interval separates the introduction of the food protein and the appearance of symptoms.

FPIAP is common in breastfed infants, accounting for as many as 60% of cases [47]. The exact prevalence is unknown, but in infants with rectal bleeding, FPIAP might account for 18–64% of cases [48, 49]. In breastfed infants, the disease usually develops later and less severely on histologic analysis [43, 47, 49]. A gradual resolution of symptoms occurs with elimination of the offending food from the mother's diet, allowing the mother to go on with breastfeeding [47].

Bleeding may persist in breastfed infants, despite maternal avoidance of food(s), probably in relation with the difficulty in removing all sources of allergen from the diet or in identifying all the responsible allergens. In these cases, a milk protein hydrolysate formula, or an amino acid-based formula, may be necessary and usually resolves bleeding, typically within 48–72 h.

The disease is typically limited but may be accompanied by colic or increased frequency of bowel movements, and sometimes increased gas (up to 30% of patients), intermittent emesis (up to 27%), pain on defecation (22%), or abdominal pain (up to 20%) may be present [1]. However, the infants typically appear well and there is no failure to thrive.

A positive family history of atopy, elevated serum IgE levels, and peripheral blood eosinophilia are sometimes seen. In stools, smears of mucus may show increased polymorphonuclear neutrophils. Mild anemia or hypoalbuminemia may develop. In the series of Lake [47], 6 of 21 patients developed iron deficiency anemia despite iron supplementation, but the weight gain was normal and the disease had disappeared within 1 year of age.

Tolerance of the offending food occurs by 1–3 years of age with the majority by 1 year. Spontaneous resolution of bleeding occurs in up to 20% of breastfed infants without changes in the maternal diet [50]. In contrast, when the maternal elimination diet seems not efficient, persistence of rectal bleeding does not hamper an excellent long-term prognosis.

Pathophysiology

FPIAP predominantly affects the rectosigmoid and the disease is typically associated with breastfeeding, meaning that the children react at the distal part of the intestine to very little amounts of the offending food. At endoscopy, lymphoid nodular hyperplasia is associated with focal erythema surrounding the lymph nodes.

Diagnosis

Diagnosis exclusively relies on the clinical history, with rectal bleeding disappearing following elimination diet, in the mother or the child, within usually 72–96 h [47], sometimes much later, underlining the need for elimination diets of at least 2–4 weeks. Persistence of occult blood is possible [48] and may suggest allergy to other unrecognized foods. An allergy workup is still necessary: even though tests for IgE-mediated food hypersensitivity are mostly inconsistent, it remains important to detect IgE-mediated milk allergies.

Exclusion of other causes of rectal bleeding, such as infection, necrotizing enterocolitis, intussusception, or anal fissure, is important (Table 4). *Campylobacter* infection is a differential diagnosis, especially since symptoms may be mild at this age, with only rectal bleeding [51]. In case of persistent bleeding, ultrasonography eliminates any anatomic abnormalities or intussusception. Importantly, the bleeding is often attributed to perirectal fissures. Typically, fissures accompanying constipation tend to present with streaks of blood on hard, formed stool, at the opposite of frothy, mucousy stools of FPIAP. However, anal fissures may be a symptom of cow's milk allergy [52–54] and thus associated with the mucosal lesions of FPIAP, which means that their presence does not rule out FPIAP and should be another argument to begin the elimination diet. There are no reports of inflammatory bowel disease in infants with FPIAP followed for

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more than 10 years, but inflammatory bowel disease may, rarely, begin during the first months of life.

Management

Treatment is dietary restriction in the mother when the child is breastfed and in the child when he or she is formula fed. Elimination is first focused on milk and dairy products. Soy formula may induce bleeding in a subset of infants reacting to cow's milk, so that it is better to eliminate also soy at least for the diagnosis period of the elimination diet. In the breastfed infants, when bleeding is not controlled by the elimination of cow's milk and soy, additional eliminations may be considered including wheat and egg. When the child is not breastfed or when the mother decides to stop breastfeeding, a milk hydrolysate may be sufficient, but the persistence of bleeding underlines the need for an amino-acid formula. Recurrence of bleeding is common when rechallenge takes place within the first 6 months. Usually, skin prick tests and the detection of food-specific IgE are negative, and food introduction takes place at home, with a gradual increase over 2 weeks.

Summary for FPIAP

FPIAP is a common condition of infancy. The prognosis is good with a majority of cases resolving in the first year of life. Cow's milk is the major offending food. Treatment relies on milk elimination, either in the mother of a breastfed infant or in the child. Accidental exposure usually triggers limited damages, e.g., relapse of rectal bleeding.

Disclosure Statement

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FOCUS

Consensus guidelines for the diagnosis of eosinophilic gastrointestinal diseases (beyond the esophagus) are required, as well as randomized controlled trials assessing the efficacy of various treatment approaches for achieving and maintaining remission while ensuring normal growth and quality of life

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Eosinophilic Gastrointestinal Diseases in Childhood

by Eleni Koutri and Alexandra Papadopoulou

Key insights

Eosinophilic gastrointestinal diseases (EGIDs) are rare chronic inflammatory disorders that affect different parts of the gastrointestinal (GI) tract. These include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC). In some cases, multiple parts of the GI tract can be affected. Although the clinical presentation varies depending on the location, histologically the EGIDs are characterized by dense eosinophilic inflammation. It is important, however, to exclude other potential causes of the GI inflammation prior to arriving at a diagnosis.

Current knowledge

EoE is the most commonly occurring and well described of the EGIDs. Nevertheless, there are no biomarkers, and diagnosis relies mainly on endoscopy and histology. Another difficulty is that the clinical symptoms vary depending on the age of the patient. EG is the second most common EGID after EoE and is characterized by dense eosinophilic infiltration of the stomach wall. EGE is more common in children below 5 years of age and nearly half of the patients have a history of allergic disease. For EC, the clinical presentation with abdominal pain and diarrhea, associated with dense eosinophil infiltration of the ileum and/or the colon in the absence of secondary causes, may aid the diagnosis. It should be noted, however, that, with the exception of EoE, there is no consensus on the diagnostic criteria for the other EGIDs.

Histological features of EGIDs

- Eosinophilic* infiltration of the lamina propria and/or submucosa, muscularis propria, or serosa
- Other findings depending on involved site of the GI tract
  - Eosinophilic surface layering
  - Eosinophilic degranulation
  - Eosinophilic crypt abscesses
  - Basal zone hyperplasia
  - Dilated intercellular spaces
  - Lamina propria fibrosis

*The histological finding of increased numbers of eosinophils per high-power field in a biopsy specimen of the GI tract has no proven biological importance and cannot be used as the only tool for the differential diagnosis of EGIDs from other GI diseases

Practical implications

Elimination diets are often used to identify potential dietary triggers, which can then be avoided. Drug therapy is tailored according to the affected segment of the GI tract. Proton pump inhibitors and topical steroids have been effective for the treatment of EoE. Corticosteroids are effective first-line treatment for EGE and EC. In the EGIDs other than EoE, thiopurines or anti-TNF drugs may be used in cases of refractory disease. Due to the chronic and relapsing nature of these diseases, maintenance treatment is needed to avoid relapses.

Recommended reading

Collins MH, Capocelli K, Yang GY. Eosinophilic gastrointestinal disorders pathology. Front Med (Lausanne). 2018 Jan;4:261.

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Annales Nestlé

Allergic or Pseudo-Allergic Gastrointestinal Disorders

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Eosinophilic Gastrointestinal Diseases in Childhood

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Key Messages

- **Eosinophilic gastrointestinal diseases (EGIDs) are rare chronic, inflammatory disorders of the gastrointestinal (GI) tract with unknown long-term sequelae. The clinical presentation depends on the involved GI site as well as the extent and the depth of eosinophilic inflammation through the bowel wall.**
- **In the absence of biological markers, the diagnosis is based on clinical symptoms and on histological findings of eosinophilic inflammation, after the exclusion of a secondary cause of inflammation or a systemic disorder, which may be a challenging issue given the absence of strict histological criteria for EGID (beyond the esophagus) diagnosis.**
- **Treatment strategies depend on the involved site of the GI tract. Maintenance treatment is often necessary to avoid relapses.**
- **Consensus recommendations on the diagnosis of EGID (beyond the esophagus), as well as randomized studies assessing the efficacy and safety of various treatment modalities, are urgently needed.**

Keywords
Eosinophilic gastrointestinal diseases · Eosinophilic esophagitis · Eosinophilic gastritis · Eosinophilic gastroenteritis · Eosinophilic colitis

Abstract
Eosinophilic gastrointestinal diseases (EGIDs) comprise a group of chronic, inflammatory diseases of the gastrointestinal (GI) tract, that are characterized, clinically, by symptoms related to the dysfunction of the involved segment(s) of the GI tract, and histologically, by dense eosinophilic inflammation, in the absence of an identifiable secondary cause. The group of EGIDs comprises eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC). EoE is the most common and the best described EGID compared to EG, EGE, and EC. The clinical presentation of the EGIDs differs depending on the location and the extent of the eosinophilic infiltration in the GI tract, as well as its depth through the bowel wall. In the absence of biological markers, the diagnosis is based on the combination of clinical symptoms with the histological features of EGIDs, after the exclusion of secondary causes of eosinophilic inflammation of the GI tract. Treatment is individualized and includes elimination diets (mainly empiric or elemental) and/or drugs, according to the involved GI segment: proton pump inhibitors or local steroids in EoE; local or oral systemic steroids in EG/EGE limited to the duodenum; oral

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systemic steroids in EGE with lower small intestine and/or colon involvement. In patients with EoE, maintenance treatment with lower doses may be considered following histological remission with the means of drugs. In patients treated with elimination diets, disease food triggers identified during food reintroduction need to be further eliminated. Esophageal stenosis despite medical treatment requires endoscopic dilation, while the use of thiopurines or anti-TNF drugs may be considered in refractory or steroid-dependent EGID (other than EoE). The aim of this review is to provide the available evidence on each of the above disorders, to aid clinicians to interpret the clinical manifestations and the laboratory findings and choose the best available treatment option.

Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are rare chronic inflammatory disorders characterized clinically by a variety of symptoms (Table 1) depending on the segment of the gastrointestinal (GI) tract involved and histologically by eosinophilic inflammation of different parts of the GI tract (Table 2), in the absence of an identifiable secondary cause (Table 3) [1].

EGIDs are subclassified into eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) depending on whether the eosinophilic infiltration is limited to the esophagus, stomach, small intestine, and colon, respectively. In some occasions, multiple parts of the GI tract can be involved, simultaneously or sequentially.

The definition, epidemiology, clinical manifestations, histological features, and treatment options of each of the EGIDs follow below.

Eosinophilic Esophagitis

EoE is a chronic immune/antigen-mediated inflammatory disease of the esophagus characterized clinically by symptoms related to esophageal dysfunction and histologically by dense esophageal inflammation [2]. The incidence of EoE is 5.1/100,000 persons/year, while the prevalence is about 29.5 cases/100,000 inhabitants [3].

The disease is more common in males and in patients with atopic diseases [4], mainly due to food allergens and aeroallergens [5], although it occurs also in patients with no history of atopy. The most common food triggers of EoE are milk, followed by wheat, soy, and eggs [4].

Clinical symptoms of EoE vary depending on age. The most common symptoms in infants and toddlers are feeding difficulties, in children vomiting and abdominal pain, while in adolescents, dysphagia and food impaction (Table 1).

Table 1. Clinical manifestations of EGIDs

EGID	Clinical symptoms
EoE	Vomiting, GERD-like symptoms, failure to thrive, dysphagia, food impaction
EG	Nausea, vomiting, retrosternal or epigastric pain, dyspepsia, hematemesis/melaena (mucosal involvement); outlet obstruction mimicking pyloric stenosis (muscular involvement)
EGE	Nausea, vomiting, abdominal pain, diarrhea, failure to thrive/weight loss, protein loss or gastrointestinal bleeding (mucosal involvement); obstructive symptoms, intussusception, perforation (muscular involvement); abdominal distention, ascites (serosal involvement)
EC	Abdominal pain, tenesmus, diarrhea with mucus and/or blood (mucosal involvement); volvulus, intussusception, perforation (transmural involvement)

Currently, there are no available specific biomarkers for the diagnosis of the disease; therefore, the diagnosis relies only on endoscopy and histology. The endoscopic findings in children with EoE vary from the presence of esophageal rings, furrows, and/or white exudates (Fig. 1a, b) to, less often, narrowing of the caliber of esophagus, although the presence of a normal esophagus does not exclude the diagnosis.

The main histological feature of EoE is dense but patchy eosinophilia of esophageal mucosa, usually associated with microabscesses, superficial layering, or extracellular eosinophil granules (Fig. 2a–c). The presence of at least 15 eosinophils per high-power field (eos/hpf), as peak value in at least one esophageal mucosal biopsy, is required for the histological definition of the disease (Table 2) [6]. The ESPGHAN recommends at least two to four esophageal biopsies to be taken from both the proximal and distal esophagus, regardless of the endoscopic appearance of the esophagus [7].

Esophageal eosinophilia is not an exclusive feature of EoE and, therefore, differential diagnosis should include other diseases that are associated with esophageal eosinophilia (Table 3).

The treatment of EoE has the following goals: (i) to achieve clinical and histological remission of the disease, (ii) to maintain remission, and (iii) to avoid iatrogenic damage. The efficacy of the treatment relies on demon-

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Table 2. Histological features of EGIDs [6, 20, 21, 26, 28, 29, 55, 56]

Eosinophilic[1] infiltration of the lamina propria and/or submucosa, muscularis propria, or serosa
– As eosinophilic inflammation is patchy, peak eosinophilic counts for the diagnosis of EGIDs are necessary The following numbers of eos/hpf have been proposed for the histological diagnosis of EGIDs, but for EGIDs beyond the esophagus, the numbers indicated below need to be confirmed by further studies in children: EoE ≥15 eos/hpf EG ≥30 eos/hpf in ≥5 hpf EGE >50 eos/hpf duodenum EC >50 eos/hpf right colon; >30 eos/hpf left/transverse colon
– Other findings Eosinophilic surface layering Eosinophilic degranulation Eosinophilic crypt abscesses Basal zone hyperplasia Dilated intercellular spaces Lamina propria fibrosis

[1] The histological finding of increased numbers of eosinophils per high-power field (eos/hpf) in a biopsy specimen of the GI tract has no proven biological importance and cannot be used as the only tool for the differential diagnosis of EGIDs from other GI diseases

Table 3. Disorders associated with GI tract eosinophilia that should be included in the differential diagnosis with EGIDs

Esophagus	GERD Infections (herpes and candida) Esophageal achalasia Crohn's disease Connective tissue disorders Hypereosinophilic syndrome Drug sensitivity response Malignancy Celiac disease
Stomach	*Helicobacter pylori* infection Inflammatory bowel disease Connective tissue disorders Hypereosinophilic syndrome
Intestine/colon	Infections (parasitic, amebic, fungal) Inflammatory bowel disease Connective tissue disorders Hypereosinophilic syndrome Vasculitis Malignancy

stration of histological and not only of clinical remission. The treatment strategies include elimination diet and/or drugs (proton pump inhibitors [PPIs] or steroids).

Three elimination diets have been used for treating EoE: (1) exclusive enteral nutrition with an amino acid-based formula (AAF); (2) empiric elimination diet; (3) targeted elimination diet. Exclusive enteral nutrition with an AAF consists of complete removal of food allergens from the diet substituted by a hypoallergenic formula based on amino acids and is reported to induce remission in up to 90% of adults and children with EoE [8]. Due to the high cost and the big number of endoscopies needed during food re-introduction, however, AAF is reserved for young infants with multiple food allergies, particularly in patients who do not respond or do not wish to follow a strict diet with multiple food elimination [7]. The targeted elimination diet is based on removal of foods detected with specific allergy testing and/or history of allergy and has limited place in the treatment of EoE, inducing remission in 45.5% of patients, because allergy testing cannot demonstrate the causative foods of the disease but only food sensitization [8]. The empiric elimination diet is based on removing the food allergens that have shown to strongly correlate with EoE from the diet. The six-food elimination diet (eliminating dairy products, soy, eggs, wheat, peanuts, fish, and shellfish) is the most studied empiric elimination diet. It has been reported to be highly effective in treating EoE, achieving histological remission in 75% of patients with EoE [8]. Recently, the four-food elimination diet, avoiding cow's milk, wheat, eggs, and legumes, was reported to achieve histological remission in 71% of children with EoE [9], while an even more recent study showed that a step-up diet strategy in treating childhood EoE is feasible: the two-food elimination diet restricting animal milk and gluten-containing cereals achieved remission in 40% of the patients with EoE, while the four-food elimination diet achieved remission in 52% and the six-food elimination diet in 65%. Amongst responders to a two-food elimination diet, the most common food triggers were animal milk and gluten-containing cereals (15%), while animal milk alone or gluten-containing cereals alone were reported in 60 and 25% of patients, respectively [10].

Based on the above findings, many clinicians prefer the step-up approach, eliminating, initially, two foods (dairy products and eggs or gluten-containing cereals), upgrading to four- and to six-food elimination in nonresponders, reserving the exclusive enteral nutrition with AAF for highly selected children. The above step-up di-

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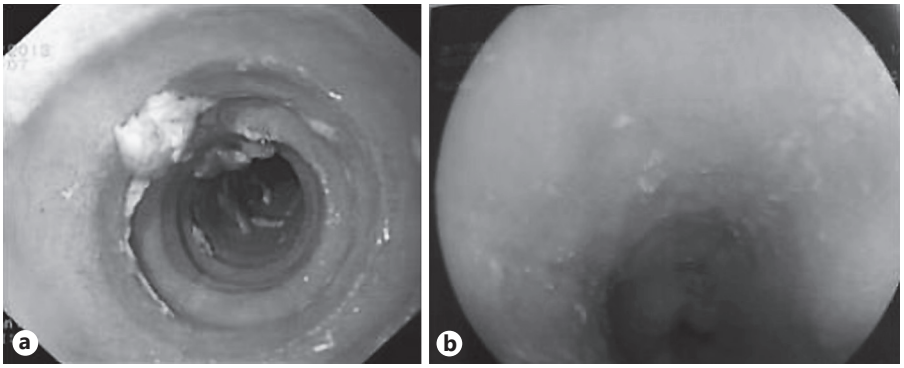

Fig. 1. a, **b** Eosinophilic esophagitis (endoscopy). **a** Trachealization of the esophagus. **b** White exudates.

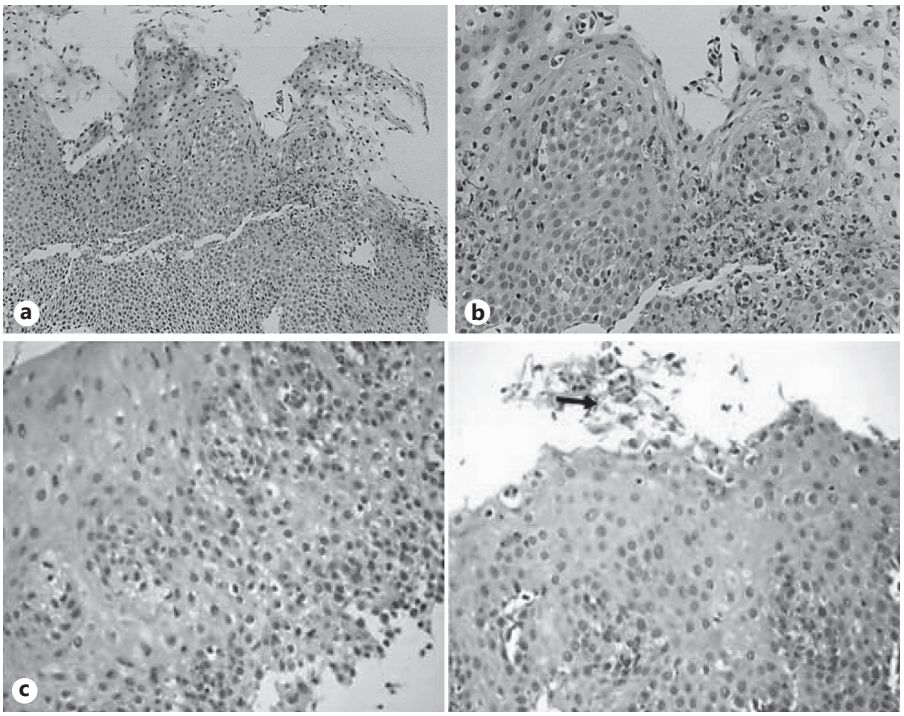

Fig. 2. a–c Eosinophilic esophagitis (histology). **a** Abscesses of eosinophils in the upper layers of the squamous epithelium. Mild /moderate hyperplasia of the basal layer. **b** Abscesses of eosinophils in the upper layers of the squamous epithelium. Severe degranulation of eosinophils. Moderate spongiosis. **c** Abscesses of eosinophils in the upper layers of the squamous epithelium (arrow).

etary strategy reduces the number of upper endoscopies and the diagnostic process time by 35%. In infants and toddlers, in whom cow's milk protein allergy is common, one-food elimination may have a place, but this has to be tested in randomized controlled trials. The use of diet treatment requires supervision by an experienced dietitian, to ensure compliance with the diet and to avoid nutritional compromise.

With regards to drug therapy of EoE, several drugs have been assessed including PPIs, corticosteroids (oral systemic and topical), cromolyn sodium, leukotriene receptor antagonists, and biologics (mainly anti-IgE and anti-IL-5 monoclonal antibodies). From the above drugs, PPIs and corticosteroids proved to be effective in treating children with EoE. PPIs have acid-suppressive but also anti-inflammatory effects and therefore may induce remission in 45% of patients with EoE [11], probably with a milder form of the disease. The recommended dose of PPIs is 1 mg/kg per dose, twice daily with the maximum dose reaching the adult dose of 20–40 mg once or twice daily depending on the patient and PPI. Oral systemic steroids are highly effective in inducing clinical and histological remission in children with EoE as early as at 2–4 weeks. Considering, however, the risks associated with the chronic use of oral systemic steroids, their use is considered only when immediate relief of the patient's symptoms such as severe dysphagia, weight loss, or esophageal stenosis, is needed. The effective dose for eliminating

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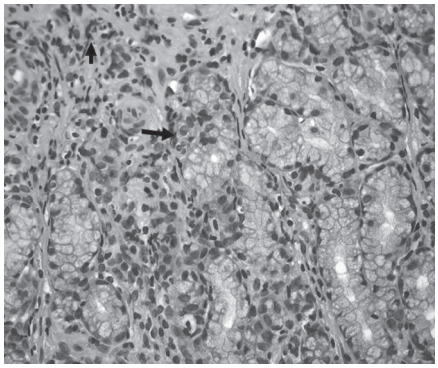

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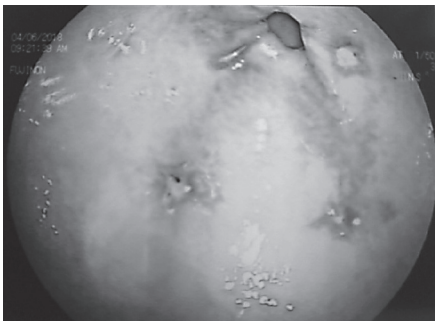

Fig. 3. Eosinophilic gastritis (histology). Aggregates of eosinophils near the muscularis mucosa (small arrow). Eosinophilic infiltration of pyloric glands (long arrow).
Fig. 4. Eosinophilic gastritis (endoscopy). Gastric antral erosions and ulcers in a child with eosinophilic gastroenteritis presenting with epigastric pain and iron deficiency anemia.

clinical symptoms and histological abnormalities is 1–2 mg/kg/day of prednisone with the maximum dose reaching 40–60 mg.

Topical steroids (swallowed fluticasone propionate and oral viscous budesonide) were assessed in patients with EoE and proved efficacy in achieving histological remission in patients with EoE as well as in maintaining remission. Fluticasone propionate is sprayed into the mouth with the lips sealed around the device and the patient is advised not to drink or eat for the next 30 min. This drug was reported to induce remission in 50% [12] to 91% of the patients [13]. The suggested dosage ranges from 88 to 440 μg twice to 4 times daily for children and from 440 to 880 μg twice daily for adolescents/adults. Oral viscous budesonide is prepared by mixing a liquid solution of budesonide 1 mg/2 mL (the preparation used for inhalations) and 5 g of sucralose. The administration of this preparation achieves histological remission in 87% of children [14] and in 72% of adolescents and adults with EoE [15]. The recommended dosage of oral viscous budesonide is 1 mg daily for children <10 years and 2 mg daily for older children and adults [6]. Viscous topical slurry is more effective than nebulized steroid therapy for patients with EoE, as it provides increased concentration of the drug in the esophagus [16]. The main side effect of topical steroids is oral candidiasis, resolving following drug discontinuation. Drug titration should be initiated after confirming histological remission following symptom resolution with a repeat endoscopy at 4–12 weeks following drug introduction. Continuation of drug therapy is needed for several months to maintain remission, but the optimal regimen, dose, and duration still need to be determined.

Other drugs that have been tested for the treatment of EoE are sodium cromoglycate or montelukast, a leukotriene receptor antagonist, but they could not demonstrate any efficacy and thus are not recommended for treating EoE. The same is true for immunomodulating drugs and biologics. The efficacy of monoclonal antibodies against IL-5 in children with EoE needs further evaluation, while anti-IgE monoclonal antibodies were effective in improving food tolerance but not in achieving histological remission [17]. Patients with severe dysphagia due to esophageal stenosis, who do not respond to medical treatment, have their symptoms relieved with endoscopic esophageal dilatation, which is performed in combination with medical treatment. Furthermore, some patients with EoE have seasonal exacerbations of the disease, caused by inhaled aeroallergens including pollens and moulds, and are often associated with food impaction [18]. In case of an established pattern of seasonal exacerbations in children with EoE, preventive measures using topical corticosteroids may be used.

In conclusion, EoE is a chronic, relapsing inflammatory disease of the esophagus which often requires prolonged therapy. Investigations and treatment need to be individualized. Further randomized studies to assess the efficacy of biological markers in disease diagnosis and prognosis, the most appropriate regimen, dosing, and duration of the maintenance therapy in different disease phenotypes, as well as the efficacy of novel agents for treating refractory disease, are urgently needed.

Eosinophilic Gastritis

EG is a clinical entity characterized by dense eosinophilic infiltration of the stomach wall. It is the second most common form of EGID after EoE, with a prevalence of about 6.3 patients per 100,000 individuals [19]. EG is found to be more prevalent among older age groups, with female predominance [19]. Furthermore, an association with documented allergic conditions was reported in 58.9% of children and in 33.6% of adults with EG [19].

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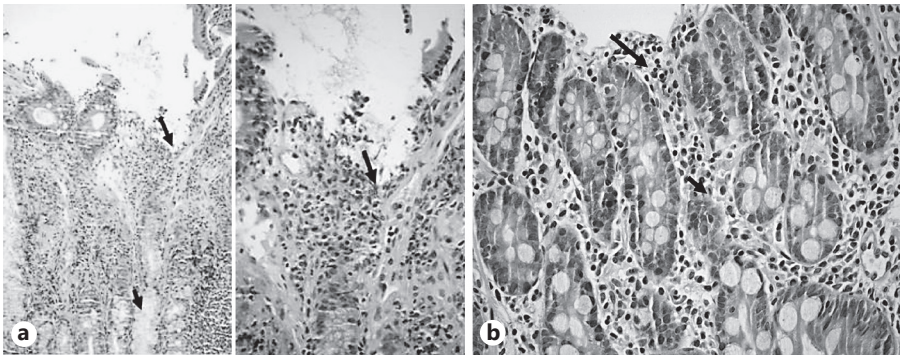

Fig. 5. a, **b** Eosinophilic gastroenteritis (histology of duodenal biopsies). **a** Erosion and aggregates of eosinophils (long arrow). Eosinophilic infiltration of the Brunner glands (small arrow). **b** Aggregates of eosinophils at the deep part of the crypts with degranulation (long arrow). Eosinophilic infiltration of the crypts (small arrow).

The histological criteria (Table 2) for the diagnosis of EG include the presence of dense eosinophilic inflammation of the gastric mucosa [20, 21], associated with eosinophil cryptitis, eosinophilic abscesses (Fig. 3), or the presence of eosinophils in the submucosa and muscularis mucosa. It has been proposed that ≥30 eos/hpf in ≥5 hpf are needed for the histological diagnosis of EG [20, 21], but this has to be confirmed by further studies in children. Furthermore, apart from the eosinophilic activation, mast cells and FOXP3-positive lymphocytes have also been reported to be activated in EG [22].

The clinical manifestations depend on the gastric layer involved in the inflammatory process. Of these, the mucosal involvement is the most common, presenting clinically with epigastric pain, nausea, vomiting, and early satiety, while the laboratory findings include peripheral eosinophilia, hypoalbuminemia, and iron deficiency anemia [23]. Furthermore, case reports in infants have attributed pyloric stenosis to EG [24] and the same was true for isolated giant ulcers resistant to PPIs, mainly in adolescent girls [25].

Endoscopy reveals nodules in the gastric mucosa, erythema and ulceration or erosions (Fig. 4), even though in some cases, the mucosa may appear completely normal [23].

Corticosteroids in their oral or topical form seem to be an effective therapy of EG. Case reports have suggested the off-label use of budesonide in the form of capsules dissolved in water, to target the upper GI tract [26], while others indicated that fluticasone led to a resolution of eosinophilic gastric inflammation when used initially to treat EoE [27].

In some children with EG, food antigen restriction may resolve both the symptoms and the histology abnormalities. Ko et al. [23] reported, in a retrospective study, that 82% of the patients with EG achieved clinical and 78% histological remission following elimination diet (elemental diet, elimination diet excluding milk, egg, wheat, soy, peanut/tree nuts, fish/shellfish, and red meat from the diet and also empiric avoidance of 1–3 foods). However, due to the fact that only up to 5 children per each dietary treatment group underwent a histological evaluation, no strict conclusions could be drawn from the above study [23]. An interesting finding in that study, however, was that although 86% of patients were found to be sensitized to several foods using skin prick tests or serum analyses, no correlation was found between response to dietary therapy and food sensitization [23].

In conclusion, EG is a chronic, relapsing disease, although its long-term outcome and clinical consequences are poorly defined. Elimination diet and/or steroids are considered as the first-line therapy for induction of remission. More studies are needed to assess the efficacy of different therapeutic approaches for maintenance.

Eosinophilic Gastroenteritis

EGE is a rare inflammatory disorder, characterized by eosinophilic infiltration of the stomach and small intestine (Fig. 5a, b), and in some cases, the esophagus and colon without any other known causes of GI eosinophilic inflammation [1].

The diagnosis of EGE is based, histologically, on the presence of a dense eosinophilic inflammation of the intestine often associated with eosinophilic degranulation [21, 28, 29]. It has been proposed that >50 eos/hpf are needed for the histological diagnosis of EGE (Table 2), but this number has to be confirmed by further studies in children. The prevalence of EGE is approximately 5.1 per 100,000 individuals [30]. EGE is more common among children of age <5 years [19]. It presents clinically with abdominal pain, abdominal distention, nausea, vomiting, diarrhea, weight loss, and sometimes with serious complications such as intestinal obstruction and perforation [31, 32].

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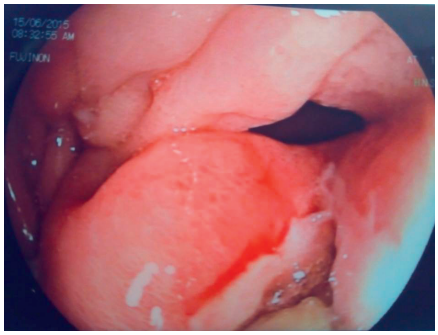

Fig. 6. Eosinophilic gastroenteritis (endoscopy). Duodenal giant ulcer in a child with eosinophilic gastroenteritis presenting with hematemesis.

Fifty-two percent of children and 41.8% of adults with EGE have a history of an allergic disease [19]. The clinical features of EGE vary according to the location, extent, and layer(s) involved in the inflammatory process [33, 34]. Mucosal disease may present with abdominal pain, nausea, vomiting, early satiety, and diarrhea, often associated with failure to thrive or weight loss. Patients with diffuse small intestine disease may develop malabsorption, anemia, and hypoalbuminemia [34]. In case of involvement of the muscular layer, eosinophilic inflammation may cause wall thickening, impaired motility, and intestinal obstruction presenting clinically with nausea, vomiting, and abdominal distention that may lead to perforation [35]. Subserosal disease is presenting with ascites [35].

As for the other EGIDs, except for EoE, there are no consensus diagnostic criteria for EGE. The diagnosis is based on the presence of GI symptoms (Table 1), eosinophilic infiltration of the GI tract (Table 2), or eosinophilic ascites on condition of the exclusion of other causes of intestinal eosinophilia (Table 3).

Laboratory findings include peripheral blood eosinophilia in 20–80% of patients [35] with an average absolute eosinophil count of 1,000 cells [36]. Mucosal and subserosal EGE are characterized by higher eosinophil counts compared to muscular EGE with an average absolute eosinophil count of 2,000 and 8,000 cells/μL, respectively. Serum albumin may be low due to protein-losing enteropathy and iron deficiency anemia may occur due to impaired iron absorption and occult GI bleeding, especially in the mucosal subtype of the disease [34]. Imaging studies in patients with the muscular subtype of the disease may reveal irregular narrowing of the gut lumen. In patients with serosal disease and ascites, ascetic fluid analysis shows a marked elevation of the eosinophil counts [34].

Endoscopic findings of EGE appear to be nonspecific and range from nodular or polypoid appearance of the mucosa to erythema, friability, and occasional ulcers (Fig. 6) or erosions [37].

Biopsies should be taken from both normal and abnormal appearing mucosa since even a normal appearing mucosa can be infiltrated by eosinophils [38]. At least 4–5 biopsies should be taken from the stomach and the small intestine, including from the macroscopically normal mucosa. Patients with muscular or subserosal type of EGE can have normal mucosal biopsies. In that case, laparoscopic full-thickness biopsy should be performed to confirm the diagnosis. Laparoscopic full-thickness biopsy should also be performed in patients with intestinal wall thickening and/or obstruction to exclude a possible underlying malignancy. The differential diagnosis of EGE includes several diseases associated with eosinophilic inflammation of the GI tract (Table 3).

Due to the rarity of EGE, there are only limited data concerning the best treatment option based on the severity of symptoms. Reed et al. [39] assessed the efficacy of various treatment modalities including dietary therapy, corticosteroids, mast cell inhibitors, H2 antagonists, and leukotriene receptor antagonists in 44 patients with EGE, including children, for an average of 26.2 months with 76% of patients needing more than one treatment option. When all treatment modalities were included, 60% of patients achieved clinical remission, while 51% achieved histological remission [39].

In symptomatic patients and in those with symptoms of malabsorption, an initial therapeutic approach could involve elimination diet [40, 41]. Gonsalves et al. [42], in a study involving adults with EGE, found a significant reduction in symptoms, complete histological remission, improvement in endoscopic findings, and normalization of peripheral eosinophilia after the six-food elimination diet or AAF within a period of 6 weeks. Katz et al. [43] reported that infants below 1 year of age, but not older children, responded well to cow's milk protein elimination diet.

Whenever dietary therapy is used, it should be supervised by an expert to assure patients' compliance and avoid nutritional compromise. Food reintroduction starts slowly, from least to most allergenic foods, following demonstration of histological remission of the disease.

Evidence to support the use of glucocorticoids in EGE is based on case series [37, 44]. Glucocorticoids are known to decrease the chemotaxis of inflammatory cells including eosinophils, decrease the release of eotaxins and other inflammatory mediators, and reduce permeability. The

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use of steroids is usually associated with a rapid improvement (within 2 weeks), regardless of the depth of inflammation through the bowel wall [44] and, therefore, a rapid tapering over the following 2–4 weeks is suggested. Fibrosis is much less common in EGE compared to EoE; therefore, oral steroids can be used at a minimum effective dose, e.g., 0.5–1 mg/kg with a maximum dose of 40 mg, while the whole duration of the treatment with oral steroids should not exceed 6 weeks. It should be noted, however, that discontinuation of steroids is often associated with disease relapse [45].

Furthermore, the use of oral budesonide suspension or the ileal releasing budesonide enteric capsules [46] crashed and dissolved in water or juice in order to reach upper GI segments has been beneficial in some patients with EGE involving the antrum and the small bowel [26], while the standard preparations are useful in case of ileum involvement. Other drugs have also been evaluated for the treatment of EGE. Sodium cromoglycate that inhibits the release of mast cell mediators and the antigen absorption in the gut or montelukast, that is a leukotriene antagonist, do not manage to induce clinical or histological remission when used as sole therapy [39]. Ketotifen (an H1-antihistamine and mast cell stabilizer), in small series of patients, improved clinical symptoms and tissue eosinophilia [47]. Humanized anti-IL-5 antibody was reported in a pilot study, to reduce peripheral and tissue eosinophilia but failed to improve symptoms, while it was associated with histological relapse after drug discontinuation [48]. Finally, thiopurines were reported to be effective in refractory cases [49], while omalizumab, an anti-IgE monoclonal antibody, was associated with improvement in symptoms but not of histological abnormalities [50]. Surgical treatment should be avoided and limited only to cases of persisted pyloric or small bowel obstruction despite treatment.

The natural history of EGE is poorly defined. Pineton de Chambrun et al. [51] reported in 43 patients with EGIDs that 18 (42%) had no relapses after initial diagnosis, 17 (37%) had multiple relapses, while 9 (21%) developed chronic disease. In patients with recurring disease, the intervals of remission between relapses ranged from months to years. Similarly, Reed et al. [39] claimed that only one-third of the pediatric and adult patients with EGE had long-lasting remission. The most common complication of the disease is GI obstruction, while fatal outcomes are fortunately rare.

To conclude, EGE is a rare inflammatory GI disease. Clinical symptoms depend on the segment of the GI tract involved as well as the extent and depth of eosinophilic infiltration through the bowel wall. The diagnosis is based on the finding of dense eosinophilic infiltration of the stomach and/or small intestine in the clinical context. First-line treatment for induction of remission includes elimination diet and/or steroids, while maintenance therapy is tailored to the individual. Long-term follow-up studies to determine the long-term outcomes of different disease phenotypes, are urgently needed.

In the absence of reliable biological markers, the diagnosis of EGIDs is based on the histological findings in biopsy specimens taken from the GI tract of symptomatic children, a quite challenging issue given the absence of strict histological criteria for EGID (apart from EoE) diagnosis

Eosinophilic Colitis

EC is a rare inflammatory GI disorder characterized clinically by symptoms related to colonic dysfunction and colon biopsies histology indicating excessive accumulation of eosinophils [52]. The prevalence of EC is estimated to be about 2.1 per 100,000 individuals [30], with no prominent differences related to age or gender [19, 30], although some authors claimed a predominance of males [53]. Associated atopy has been reported in 52.0% of pediatric patients and in 35.9% of adults with EC [19].

Common histological abnormalities found in colonic biopsies from patients with EC include increased eosinophilic density (Fig. 7), eosinophilic cryptitis or crypt abscesses, crypts architecture impairment, increased intraepithelial eosinophils, and/or the presence of eosinophils in the muscularis mucosa and submucosa [54].The histological criteria for diagnosing EC in adults include the presence of at least 100 eos/hpf in the cecum and ascending colon, 84 eos/hpf in the transverse and descending colon, and 64 eos/hpf in the rectosigmoid area [21]. In children, there is no consensus on the cutoff number of eosinophils for EC diagnosis, although numbers above 50 eos/hpf [55] depending on the site of the colon, in the clinical context, may aid the EC diagnosis, but this needs to be confirmed by further studies in children.

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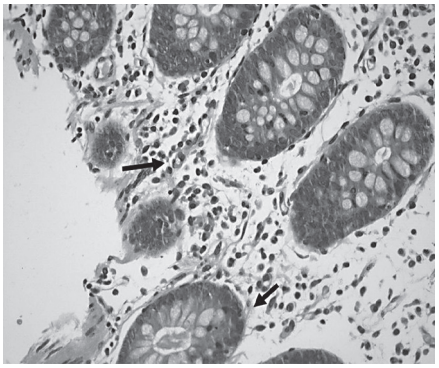

Fig. 7. Eosinophilic colitis (histology). Aggregates of eosinophils at the deep part of the colonic crypts with degranulation (long arrow). Eosinophilic infiltration of colonic crypts (small arrow).

The most common symptoms of EC (Table 1) are abdominal pain and diarrhea, while volvulus or intussusception have also been reported [56]. Endoscopic findings include mucosal granularity, erythema, the presence of ulcers or erosions, and/or white exudates.

EC is thought to be an enigmatic disease since several studies have documented the presence of eosinophilic infiltration in colonic biopsies of patients with allergy or inflammatory bowel disease [57]. The presence of inflammatory cell populations in combination with excessive eosinophilic infiltration may raise the suspicion of inflammatory bowel disease, while the presence of deposits of both IgE and tryptase in perineural areas may raise the suspicion of EC [58]. Furthermore, colonic tissue eosinophilia can also be found in patients with other disorders that need to be considered in the differential diagnosis (Table 3).

The most effective treatment of EC are corticosteroids. It should be noted, however, that a subgroup of patients, mainly infants or young children, may also benefit from the elimination diet [59], while the use of anti-TNF biological drugs such as infliximab or adalimumab may achieve long-lasting remission in refractory disease [60].

Conclusions

EGIDs are emerging chronic, inflammatory disorders in childhood with largely unknown long-term consequences. Their clinical presentation depends on the GI layer involved, the extend of the inflammation in the GI tract, and the depth of the eosinophilic inflammation through the bowel wall. In the absence of reliable biological markers, the diagnosis of EGIDs is based on the histological findings in biopsy specimens taken from the GI tract of symptomatic children, a quite challenging issue given the absence of strict histological criteria for EGID (apart from EoE) diagnosis. The exclusion of secondary causes of GI inflammation is critical. Therapeutic approaches are based mainly on case reports and small series of patients. First-line therapy includes elimination diets and/or drugs that are chosen depending on the involved GI segment. International, consensus recommendations on EGID diagnosis are urgently needed, in order to facilitate high-quality randomized controlled trials to assess the efficacy of various treatment approaches for achieving and maintaining remission while ensuring normal growth and quality of life.

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FOCUS

Frequently, there is confusion between lactose intolerance and CMA, which could result in unnecessary dietary restriction or avoidable reactions

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Lactose Intolerance: Common Misunderstandings

by Margherita Di Costanzo and Roberto Berni Canani

Key insights

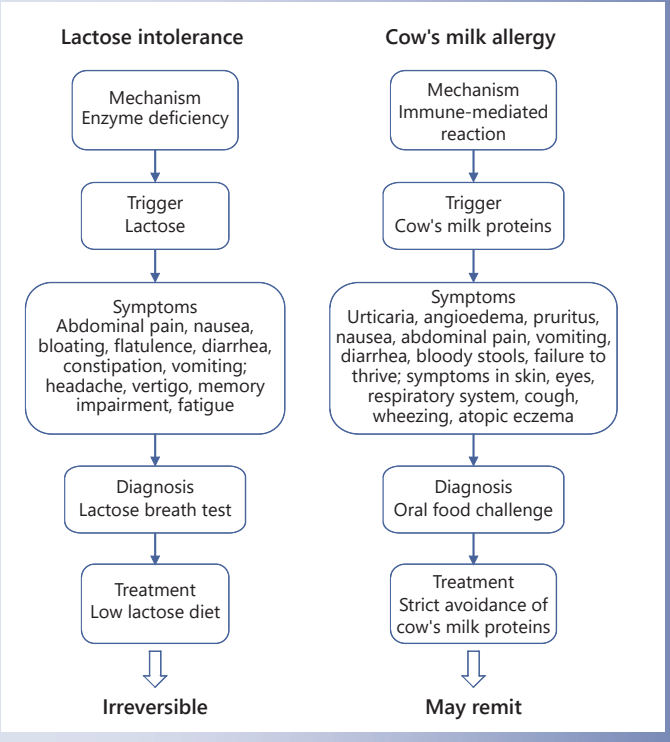
Lactose intolerance is a syndrome that consists of the manifestation of one or more symptoms upon consumption of lactose-containing foods. Although it is one of the most common forms of food intolerance, lactose intolerance is often confused with cow's milk allergy (CMA) and is wrongly labelled as "milk allergy." This is often due to the overlapping symptoms such as abdominal pain, bloating, flatulence, and diarrhea. This review highlights the fundamental differences between lactose intolerance and CMA and explains how this knowledge guides the diagnosis and management of these conditions.

Current knowledge

Lactose intolerance arises from insufficient levels of lactase activity in the brush border of the small intestinal mucosa. The most common is primary lactose intolerance (also known as lactase non-persistence), where lactase expression drops sharply in later childhood or adolescence. Around 70% of the global population is affected. The undigested lactose in the intestinal tract results in osmotic diarrhea and microbial fermentation of lactose. These events produce the clinical symptoms such as abdominal pain, flatulence, nausea, and diarrhea. In contrast, CMA is mediated by the immune system. IgE- or non-IgE-mediated reactions occur between 2 and 48 h after ingestion. The symptoms of CMA are often wrongly attributed to intolerance.

Practical implications

A thorough medical history, anamnesis, and the lactose breath test are the mainstays for identifying adult-type lactose intolerance. Genetic testing is necessary to identify patients with rare congenital mutations in the lactase phlorizin hydrolase (LPH) gene. In addition, the presence of other conditions that may affect the gut or the intestinal microbiota should be ruled out (such as infections, Crohn's disease, or celiac disease). Once diagnosed, the primary treatment strategy for those with lactose intolerance is to limit the intake of lactose-containing foods. In contrast, those with a bona fide CMA should strictly avoid cow's milk-derived foods in their diet.



Summary of the main differences between adult-type lactose intolerance and cow's milk allergy

Recommended reading

Walsh J, Meyer R, Shah N, Quekett J, Fox AT. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations. Br J Gen Pract. 2016 Aug;66(649):e609–11.

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Allergic or Pseudo-Allergic Gastrointestinal Disorders

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Lactose Intolerance: Common Misunderstandings

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Key Messages

- **Lactose intolerance is often confused with cow's milk allergy by patients and parents.**
- **A better knowledge of the differences between these clinical conditions could limit misunderstandings in the diagnostic approach and management.**

Keywords
Adverse food reactions · Food intolerance · Lactase · Cow's milk allergy · Breath test

Abstract
Lactose intolerance primarily refers to a syndrome having different symptoms upon the consumption of foods containing lactose. It is one of the most common form of food intolerance and occurs when lactase activity is reduced in the brush border of the small bowel mucosa. Individuals may be lactose intolerant to varying degrees, depending on the severity of these symptoms. When lactose is not digested, it can be fermented by gut microbiota leading to symptoms of lactose intolerance that include abdominal pain, bloating, flatulence, and diarrhea with a considerable intraindividual and interindividual variability in the severity of clinical manifestations. These gastrointestinal symptoms could be similar to cow's milk allergy and could be wrongly labeled as symptoms of "milk allergy." There are important differences between lactose intolerance and cow's milk allergy; therefore, a better knowledge of these differences could limit misunderstandings in the diagnostic approach and in the management of these conditions.

Introduction

The signs and symptoms of adverse food reactions (AFRs) in children derive from several mechanisms (see Fig. 1) [1]. These mechanisms can be triggered by different components of the same food. Immune-mediated reactions (i.e., food allergy, celiac disease) are elicited by food proteins, whereas the vast majority of non-immune-mediated AFRs derive from carbohydrate intolerances (see Fig. 2). The most common carbohydrate intolerance in the pediatric age is lactose intolerance. During infancy, lactose accounts for most of the dietary carbohydrates. Lactose is a disaccharide, which is present in many dairy products, composed by galactose linked to glucose via a β-1→4 glucosidic bond. Lactose is hydrolyzed by β-galactosidase (lactase) bound to the small intestine brush border membrane, then the monosaccharides glucose and galactose are both actively absorbed in the small intestine. Lactose intolerance primarily refers

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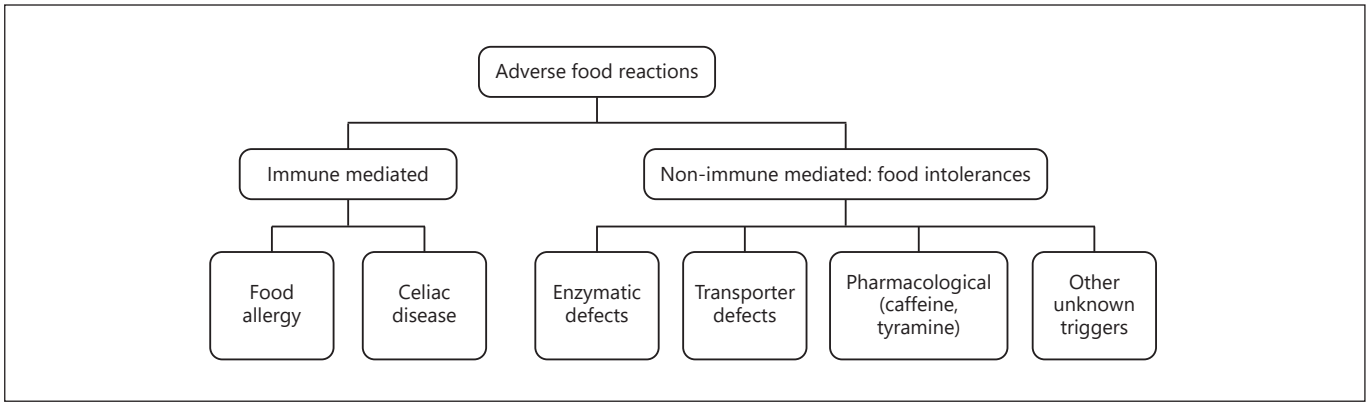

Fig. 1. Classification of adverse food reactions.

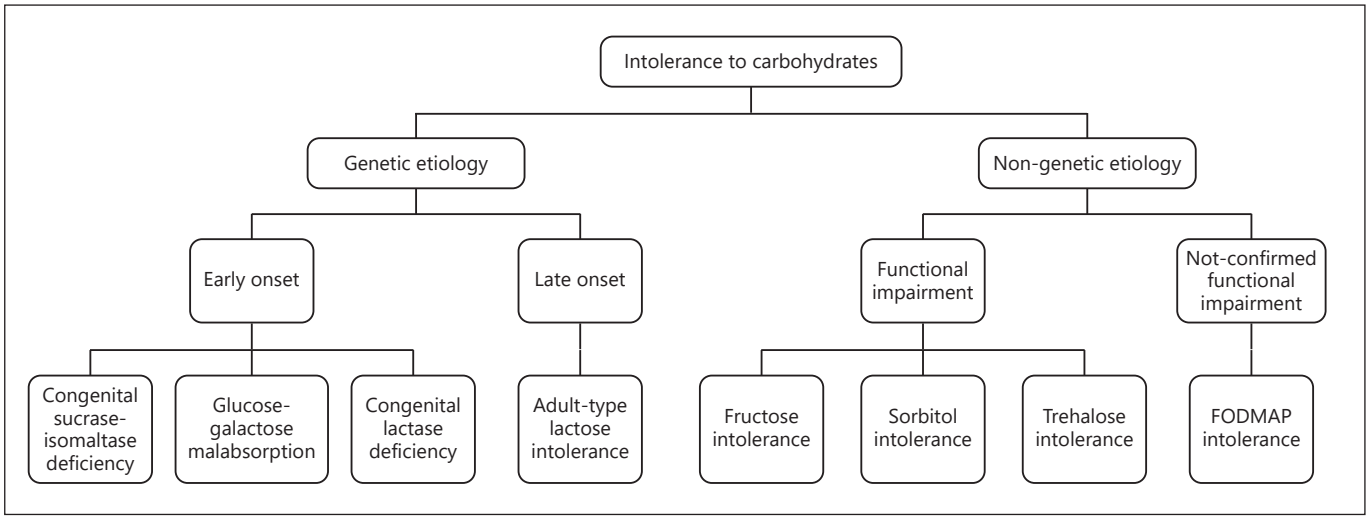

Fig. 2. Classification of carbohydrate intolerances.

to a syndrome having different intestinal or extraintestinal symptoms upon the consumption of foods containing lactose that derives from an insufficient level of lactase activity in the brush border of the small bowel mucosa [2].

Three Types of Lactose Intolerance

Different factors cause the lactase deficiency underlying each type:

1. Congenital lactase deficiency (CLD): an extremely rare autosomal recessive disease characterized by absent or reduced enzymatic activity from birth.
2. Primary lactose intolerance or adult-type lactase deficiency: a common autosomal recessive condition resulting from a developmentally regulated change of the lactase gene expression.
3. Secondary lactase deficiency: a transient condition deriving from intestinal damage secondary to several diseases such as infections, food allergy, celiac disease, small bowel bacterial overgrowth, Crohn's disease, or radiation/chemotherapy-induced enteritis.

CLD is a rare (only a few cases have been described) and severe intestinal autosomal recessive disease, within the group of congenital diarrheal disorders, caused by the absence of lactase activity from birth (OMIM 223000) [3, 4]. This condition must be distinguished from the developmental lactose intolerance that could be observed in premature infants. These subjects may have reduced levels of lactase because small intestinal lactase-

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expressing enterocytes develop later in the third trimester. The main symptoms of CLD are watery diarrhea, intestinal meteorism, and malnutrition, beginning on the first days after birth with the onset of lactation with breast milk or lactose-containing formula. Symptoms disappear when patients change to a lactose-free diet. The typical feature of CLD is the absence or very low levels of lactase expression deriving from a mutation in lactase phlorizin hydrolase gene (LPH) located on 2q21.3 [5, 6]. Most CLD cases have been described in Finland, where the disorder is enriched due to a founder effect and genetic drift [5, 7]. Premature stop codons and a truncated protein as a result of frame shifts, missense mutations in the coding region of LPH, or exon duplication are the most common genotypes identified in these patients [7–10]. Some other cases include mutations leading to single amino acid substitutions that can interfere with the proper maturation and function of LPH [7, 11]. More recently, severe forms of CLD elicited by mutations in the LPH gene that occur in either a compound heterozygous or homozygous pattern of inheritance have been described [3].

In primary lactose intolerance, intestinal lactase expression falls off sharply, making dairy products difficult to digest later in childhood or adolescence. It is the most common type of lactose intolerance and it is genetically determined. Approximately 70% of the global adult population are lactase non-persistent (hypolactasia). The global distribution and the age at which lactase expression declines vary with ethnicity. In South America, Africa, and Asia, more than 50% are lactase non-persistent. The condition is also common in Mediterranean or Southern European populations. In some Asian countries, up to 100% are lactase non-persistent. In the United States, the percentage of lactase non-persistence varies with ethnic origin with the lowest percentage in the population of European origin and the highest percentage in Hispanics and in the Afro-American population. People who develop primary lactose intolerance start life producing plenty of lactase, a necessity for infants, who get all their nutrition from milk. As children replace milk with other foods, their lactase production decreases. Children of African, Asian, or Hispanic descent may experience symptoms beginning between the age of 2 and 3 years, whereas subjects of European and American descent typically do not develop symptoms of lactose intolerance until later in childhood (5–6 years of age) or adolescence [12–14]. Lactase persistence is inherited as a dominant Mendelian trait [15]. The genetic trait of persistence of intestinal lactase expression can be caused by five or more independent single nucleotide variants in a regulatory region (a transcriptional enhancer) upstream of the lactase gene. One of these, −13910*T (rs4988235) is responsible for most cases of lactase persistence in Caucasian individuals, others such as −13907*G (rs41525747), −13915*G (rs41380347), −14009*G (rs869051967), and −14010*C (rs145946881) are found at variable frequencies in the Middle East and Africa [16, 17]. Several individual variables can influence the development of symptoms in non-persistence lactase subjects: dose of lactose in diet, intestinal transit time, lactase expression, distribution and fermentation ability of gut microbiota, sensitivity towards chemical and mechanical stimulation of the gut, and psychological factors [18–20]. Adaptation of gut microbiota, assuming a growing dose of lactose, with increase of bacterial β-galactosidase activity is recognized as a cause of symptom reduction in lactose intolerance [21, 22].

All pathological conditions that cause small intestine damage can induce a reduction in lactase expression determining a secondary and transient lactase deficiency

Lastly, virtually all pathological conditions that cause small intestine damage can induce a reduction in lactase expression determining a secondary and transient lactase deficiency. Among the diseases associated with secondary lactose intolerance there are celiac disease, small bacterial overgrowth, and Crohn's disease. Treatment of the underlying disorder may restore lactase levels and improve signs and symptoms, though it can take time. Abdomen radiation therapy or chemotherapy could also lead to lactose intolerance. Cow's milk allergy (CMA) can cause severe enteropathy with secondary lactase deficiency. In these patients, there may be an overlap of gastrointestinal symptoms due to CMA and lactose intolerance. Therefore, the same food, such as cow's milk, can lead to an adverse reaction through different mechanisms.

Differences between Lactose Intolerance and CMA

Frequently, among both patients and physicians, there is confusion between lactose intolerance and CMA, which could result in unnecessary dietary restriction or avoid-

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Table 1. Main differences between (adult-type) lactose intolerance and cow's milk allergy

	Lactose intolerance	Cow's milk allergy
Mechanism	Enzyme deficiency	Immune-mediated reaction
Onset of symptoms	5–6 years of age	Peaks during the first year of life
Resolution	Irreversible	Tending to remit in childhood (2–5 years of age)
Food component involved	Lactose, the primary digestible carbohydrate found in mammalian milk, including human milk	Cow's milk proteins
Eliciting doses	Grams	From nanograms to milligrams
Gastrointestinal symptoms	Abdominal pain, nausea, bloating, flatulence and diarrhea (less common: constipation, vomiting)	*IgE-mediated:* urticaria, angioedema of the lips, tongue, and palate; oral pruritus; nausea; colicky abdominal pain; vomiting; diarrhea *Non-IgE-mediated:* vomiting, diarrhea, blood and/or mucus in the stools, abdominal pain, malabsorption often associated with failure to thrive or poor weight gain
Extraintestinal symptoms	Headache, vertigo, memory impairment and lethargy	*IgE-mediated:* skin (acute urticaria and/or angioedema); respiratory system (nasal itching, sneezing, rhinorrhea, or congestion, and/or conjunctivitis, cough, chest tightness, wheezing, or shortness of breath); other (signs or symptoms of anaphylaxis) *Non-IgE/IgE-mediated:* atopic eczema
Test to confirm the diagnosis	Lactose breath test	Oral food challenge
Dietary treatment	Low lactose diet	Cow's milk proteins-free diet

able reactions. "Milk allergy," "milk intolerance," and "lactose intolerance" are often used by patients and their parents without a clear sense of the different meanings, understanding of the different mechanisms that underlie them, or the dietary implications of the diagnosis. The management of these conditions is distinctly different, and inappropriate recognition or management may have significant implications for the patient [23].

Lactose intolerance results from a reduced ability to digest lactose, a sugar. As explained above, lactose intolerance is a "non-immune-mediated AFR," while CMA is one of the most common forms of food allergy ("immune-mediated AFR") in particular in the first years of life. CMA may be due to immunoglobulin E (IgE), non-IgE mediated, or mixed reactions. After food intake, IgE-mediated reactions typically occur within 2 h, whereas non-IgE-mediated reactions develop after 2–48 h or some days after the food ingestion [24]. In particular, the symptoms of non-IgE-mediated CMA are frequently wrongly labeled as symptoms of intolerance. The main differences between CMA and lactose intolerance are summarized in Table 1.

Clinical Symptoms of Lactose Intolerance

Non-digested lactose in the intestinal tract drives fluids into the gut lumen through an osmotic force, causing osmotic diarrhea. Moreover, gut microbiota fermented lactose, producing volatile fatty acids and gases (hydrogen, methane, and carbon dioxide). All these events are responsible for the clinical symptoms, such as distension of the small bowel, non-focal abdominal pain associated with bloating and flatulence, nausea, increased gut motility, and diarrhea [25]. These symptoms usually develop from 30 min to 2 h after the ingestion of lactose-containing foods. Food intolerances have long been reported by patients with functional gastrointestinal disorders; however, randomized controlled trials are lacking in this area [26]. Extraintestinal symptoms, such as headache, vertigo, memory impairment, and lethargy, have been described in up to 20% of subjects with carbohydrate intolerance [27]. These systemic symptoms could be the result of toxic metabolites, produced by sugar fermentation of colonic bacteria that can alter cell-signaling mechanisms [28]. However, it is unclear whether these atypical symp-

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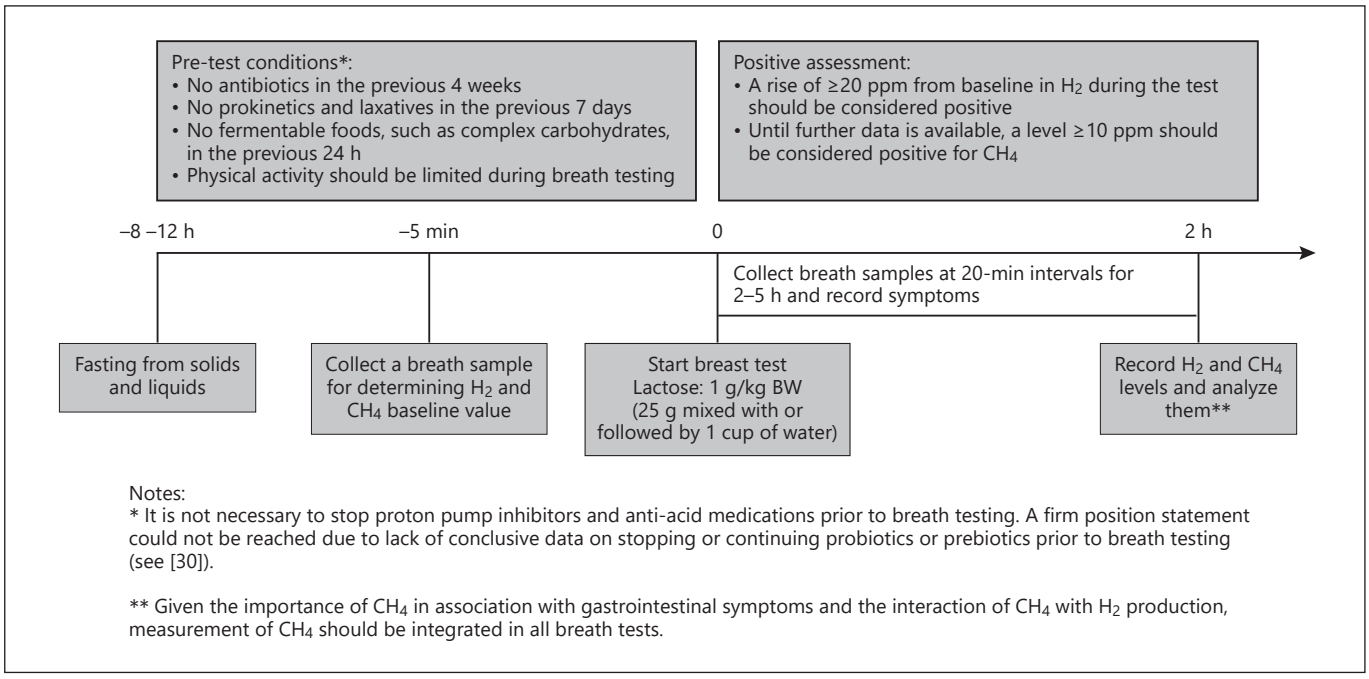

Fig. 3. Lactose breath test procedure in children with suspected lactose intolerance.

toms are directly due to lactose ingestion or related to the presence of the so-called "functional disease," frequently accompanied by multiple somatic complaints [17].

Diagnostic Approach to a Pediatric Patient with Suspected Lactose Intolerance

Genetic testing for mutations of the LPH gene should be performed whenever CLD is suspected in infants with typical symptoms and a positive response to dietary elimination of lactose [29]. In secondary lactase deficiency, a good clinical history often reveals the relationship between lactose ingestion and symptoms. The mainstays of adult-type lactose intolerance diagnosis are anamnesis and the lactose breath test (LBT) [17]. The LBT is a rapid, non-invasive test that allows measuring the content of hydrogen in the expired air. The dose of lactose administered is 1 g/kg in children. Although high doses of lactose (≥50 g) have been used for LBT, 25 g (equivalent of 500 mL of milk) is within the normal range of consumption and is the recommended dose after 8–12 h of fasting [30]. All breath testing should incorporate measurement of CO_2 (or O_2) to adjust the breath sample for non-alveolar dilution of exhaled air [31]. Concomitant measurement of CH_4 is also required because the detection rate of an early rise in H_2 production significantly decreases in excess methane producers [30]. A cutoff increase of H_2 of 20 parts per million (ppm) above the baseline level is considered as positive (CH_4 ≥10 ppm) (see Fig. 3).

Factors that may produce false-negative or false-positive results include conditions affecting the gut microbiota (e.g., recent use of antimicrobial agents), lack of hydrogen-producing bacteria (10–15% of the population), ingestion of high-fiber diets before the test, small intestinal bacterial overgrowth, or intestinal motility disorders [17, 32].

Another diagnostic test, quite popular in the past, is the lactose tolerance test. In this test, the patient suspected to have lactose intolerance assumes 50 g of lactose dissolved in water. Samples of capillary blood are taken to test the plasma glucose concentration at −5, 0, 15, 30, 45, and 60 min. A maximal plasma-glucose increase of 1.4 mmol/L or higher indicates lactose tolerance [33]. The lactose tolerance test is not sensitive enough; it is also often falsely positive because of lack of an increase of blood glucose concentration attributable to a normal insulin response to the carbohydrate load. Given the high rate of false-negative and false-positive results, this test should not be used and has been replaced by the LBT [34].

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Table 2. Lactose content in common dairy foods

Food	Lactose, g/100 g of food
Skimmed cow's milk	4.7
Low-fat cow's milk	4.6
Whole cow's milk	4.5
Buttermilk	4.1
Lactose-free milk	0.5
Whole powdered milk	35.1
Skimmed powdered milk	50.5
Goat's milk	4.2
Buffalo milk	4.9
Yogurt	3.2
Butter	4.0
Cottage cheese	2.6
Mozzarella cheese	1.5–2.0
Goat cheese	1.5–2.0
Ricotta cheese	4.0
Parmigiano Reggiano cheese	0–0.9
Cream cheese	6.0
Taleggio cheese	0
Fontina cheese	0
Provolone cheese	0
Gorgonzola cheese	0

Table 3. Low-lactose diet

Food to limit
– All kinds of milk: whole, low fat, non-fat, cream, powdered, condensed, evaporated, goat, acidophilus, and chocolate
– Butter, cottage cheese, ice cream, creamy/cheesy sauces, cream cheeses, soft cheeses (brie, ricotta), mozzarella, whipped cream, yogurt
– Fish and meat (breaded or creamed)
– Milk bread, crackers, creamed, scalloped, or au gratin potatoes
– Muffin, biscuit, waffle, pancake, and cake mixes; milk chocolate; bakery products and desserts that contain the ingredients listed above
Foods allowed
– Lactose-free milk, soy milk
– Lactose-free dairy, hard cheeses (Parmigiano Reggiano, Pecorino, Grana Padano, fontina, taleggio, provolone, Swiss), gorgonzola
– All fruits
– All vegetables
– All legumes
– All cereals
– All meat, fish, and eggs
– All vegetable fats

The genetic test, identifying single nucleotide polymorphism associated with lactase persistence/non-persistence, is also available. It should be noted that the presence of the lactase non-persistent gene does not imply the simultaneous presence of lactose intolerance that may appear later in life.

Management of Lactose Intolerance and Nutritional Issues

The mainstay of treatment for AFRs is to eliminate the causative food from the diet. In the AFRs induced by CMA, also small protein doses can cause symptoms, so the management is based on the strict avoidance of the cow's milk-derived allergenic peptides in the diet. On the contrary, a reduction of lactose intake rather than full exclusion is recommended in lactose intolerance, because available data suggest that adolescents and adults can usually ingest up to 12 g of lactose in a single dose (equivalent to 1 cup of milk, corresponding to 240 mL) with no or minimal symptoms [35]. So, in these patients dietary treatment consists only in a low-lactose diet (Tables 2, 3) [2, 35]. There is no scientific evidence to identify the tolerable dose of lactose for children with lactose intolerance. Determining the amounts of lactose that can be tolerated is necessary to develop evidence-based dietary recommendations that meet the needs of the individual. In primary lactose intolerance, lactose-containing dairy products are generally avoided for 2–4 weeks, the time required to induce symptom remission. Then, a gradual reintroduction of dairy products low in lactose up to a threshold dose of individual tolerance should be recommended.

In secondary hypolactasia, a restricted diet is necessary only for a limited time [35]. Concern about lactose intolerance and osmotic diarrhea in the treatment of undernourished children has led to a restricted use of lactose in these patients. Even in well-nourished children, low-lactose formulas are frequently used in children with persistent diarrhea. It is useful to find a balance where the amount of lactose in food does not induce osmotic diarrhea, but can help to achieve the beneficial effects of lactose. Clinical trials are needed to better define the safe and appropriate lactose dietary levels for moderately and severely undernourished children [36]. In the rare form of CLD, a complete lactose-free diet is required for life.

Enzyme replacement is another therapeutic approach in patients with lactose intolerance that wish to enjoy dairy products. Preliminary data showed an improvement of gastrointestinal symptoms and a decrease of H_2 levels at breath test with the administration of 1,500 U/day of β-galactosidase. However, more data regarding the efficacy of this micro-

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bial exogenous enzyme are needed [37]. Other evidence suggested that efficacy of exogenous lactase was obtained from *Kluyveromyces lactis*, *Aspergillus oryzae*, or *Kluyveromyces lactis* [38, 39]. Another strategy involves probiotics that could shape gut microbiota composition. Four-week consumption of a mix probiotic combination (*Lactobacillus casei* Shirota and *Bifidobacterium breve*) improved symptoms and decreased H_2 production in lactose-intolerant patients. These effects appeared to be persistent for at least 3 months after suspension of probiotic consumption [40], and strain-specific because in a similar study a milk containing *L. acidophilus* resulted ineffective [41]. A randomized, double-blind, placebo-controlled trial conducted in adult lactose-intolerant patients demonstrated that a 36-day treatment with a highly purified (>95%) short-chain galactooligosaccharide (GOS), designated "RP-G28" (escalating doses from 1.5 to 15 g/day) plus subsequent dairy consumption significantly improved clinical outcomes for lactose digestion and tolerance. These clinical outcomes correlated with a significant modification in gut microbiota composition consisting of an increase in lactose-fermenting *Bifidobacterium*, *Faecalibacterium*, *Lactobacillus*, and *Roseburia* [42]. Further studies are required to provide high-quality evidence to support or compare the efficacy of all these strategies.

In the management of lactose-intolerant patients, it is important to consider that lactose intolerance can be part of a wider intolerance to variably absorbed, fermentable oligo-, di-, monosaccharides and polyols (FODMAPs). This is present in a high percentage of patients with irritable bowel syndrome and this group requires not only restriction of lactose intake but also a low-FODMAP diet to improve gastrointestinal symptoms [17].

"Free" diets are in fashion. In supermarkets tons of products labeled lactose-free can be easily found; there are more and more cafes, ice-cream shops, bakeries, and restaurants offering special menus, where lactose has been banished. Milk consumption is decreasing in the USA and is the lowest in countries with a high prevalence of lactase non-persistence [14]. Indeed, the National Health and Nutrition Examination Survey (NHANES) reported approximately 5% of infants received lactose-reduced formulas in the USA alone between 2003 and 2010, and this trend is increasing [43]. A common rationale for the use of lactose-free infant formulas is that infants are presumed to be lactose intolerant; although there is little or no evidence that lactose-reduced formulas are beneficial [44]. Preliminary evidence shows that elimination of lactose from the infants' diet is disadvantageous for the development of healthy gut microbiome [45] and a different plasma metabolic profile in lactose-free formula-fed children [46]. A lactose-free diet should be prescribed only when a true diagnosis of lactose tolerance is achieved. A full dairy exclusion diet may also affect other health outcomes. It is important to underline that if dairy products are eliminated, other dietary sources of calcium or calcium supplements need to be provided. The current recommendations for calcium intake are 700 mg/day for children aged 4–9 years, and 1,300 mg/day over 10 years, according to the EFSA guidelines [47]. Educational and commercial efforts to improve calcium and vitamin D intake are now focusing on stimulating the consumption of tolerable amounts of milk, use of lowered lactose-containing foods including hard cheeses, yogurt, and lactose-hydrolyzed milk products.

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FOCUS

The notion of gluten as sole trigger of NCGS is too restrictive; recent clinical trials indicate that other food components such as FODMAPs also play an important role

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Non-Celiac Gluten Sensitivity: A Challenging Diagnosis in Children with Abdominal Pain

by Frank M. Ruemmele

Key insights

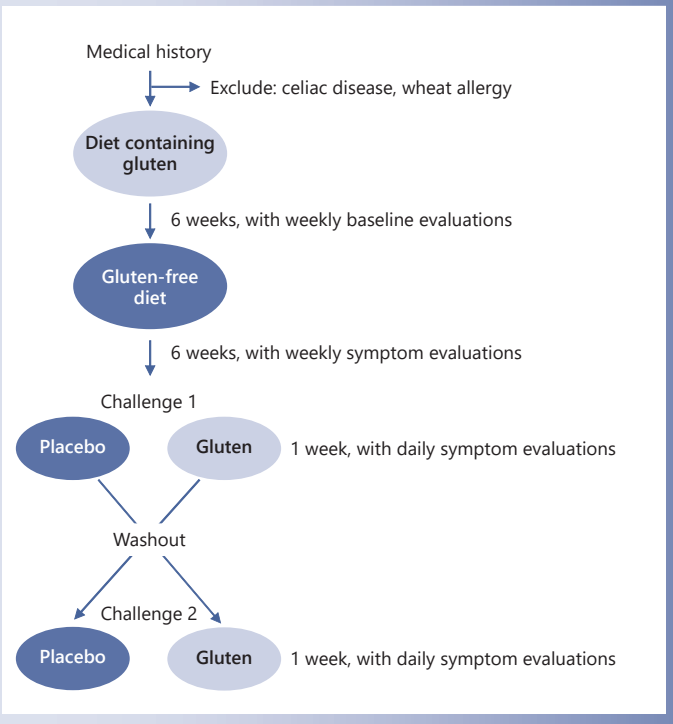
Gluten ingestion can cause a series of distinct clinical disorders with overlapping symptoms. These disorders are celiac disease, wheat allergy, and non-celiac gluten sensitivity (NCGS). Celiac disease and wheat allergy are widely recognized among pediatricians. In contrast, NCGS is not as well known. NCGS is a syndrome of intestinal and extraintestinal manifestations that occur in response to the ingestion of gluten. Recent data, however, point towards other components of wheat, such as amylase/trypsin inhibitors, wheat germ agglutinins, or fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) that may also trigger clinical symptoms.

Current knowledge

The clinical presentation of NCGS consists of highly variable intestinal and extraintestinal symptoms. Bloating and abdominal pain are common, followed by diarrhea, epigastric pain, and nausea. Many also report headache, tiredness, anxiety, skin rash, and muscle/joint pains. Clinicians should be aware that many of these overlap with classical celiac disease and other diseases such as irritable bowel syndrome. Thus far, the main diagnostic test is the double-blind, placebo-controlled gluten challenge with a crossover.

Practical implications

The difficulties in diagnosis is a reflection of the complex pathophysiology of NCGS. No specific gluten peptide has been identified as being reproducibly associated with NCGS. Once a link between gluten ingestion and the clinical symptoms has been established, the patient should follow a strict gluten-free diet for several weeks to months. To further complicate matters, other wheat components, such as fructan, are also present in many fruits and vegetables. Therefore, it is possible that we may see an increase in the spectrum of different foods associated with NCGS. For the patient, repeat challenges are sometimes necessary in order to clarify the clinical situation.



Key steps in the diagnosis of non-celiac gluten sensitivity.

Recommended reading

Catassi C, Elli L, Bonaz B, Bouma G, Carroccio A, Castillejo G, et al. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. Nutrients. 2015 Jun;7(6): 4966–77.

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Allergic or Pseudo-Allergic Gastrointestinal Disorders

Annales Nestlé

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Non-Celiac Gluten Sensitivity: A Challenging Diagnosis in Children with Abdominal Pain

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Key Messages

- **Gluten ingestion can cause different overlapping clinical disorders: three distinct entities are recognized: celiac disease, wheat allergy, and non-celiac gluten sensitivity.**
- **The incidence of non-celiac gluten sensitivity is steadily increasing in adults as well as in children and adolescents.**
- **Non-celiac gluten sensitivity is a syndrome of intestinal and extraintestinal manifestations in response to the ingestion of gluten; however, newer data indicate that other components of wheat, such as amylase/trypsin inhibitors, wheat germ agglutinins, or FODMAPs, may also cause clinical symptoms. FODMAPs are present in many nutrients other than cereals.**

Keywords
Gluten · FODMAPs · Irritable bowel syndrome · Gluten sensitivity · Pediatrics

Abstract
Several disorders related to the ingestion of gluten are well recognized despite overlapping clinical presentations: celiac disease, an autoimmune enteropathy triggered by gluten ingestions in susceptible individuals, allergy to wheat, and more recently non-celiac gluten sensitivity (NCGS). While celiac disease and wheat allergy are well-known disorders with a clear-cut diagnosis based on clinical tests and biological parameters, NCGS is a more difficult diagnosis, especially in children with functional gastrointestinal (GI) complaints. NCGS is considered a syndrome of intestinal but also extraintestinal symptoms occurring within hours, but sometimes even after several days of gluten ingestion. In children, the leading symptoms of NCGS are abdominal pain and diarrhea, while extraintestinal symptoms are rare, in contrast to adult patients. No precise diagnostic test nor specific biomarkers exist, except a rather cumbersome three-phase gluten-exposure, gluten-free diet, followed by a blinded placebo-controlled gluten challenge with crossover to provoke symptoms elicited by gluten in a reproducible manner that disappear on gluten-free alimentation. Recent data indicate that the peptide part of wheat proteins is not necessarily the sole trigger of clinical symptoms. Mono- or oligosaccharides, such as fructan and other constituents of wheat, were able to provoke GI symptoms in clinical trials. These new findings indicate that the term gluten sensitivity is probably too restrictive. The incidence of NCGS was reported in the range of 1–10% in the general population and to increase steadily; however, most data are based on patients' self-reported gluten intolerance or avoidance without a medically confirmed

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diagnosis. Treatment consists of gluten avoidance for at least several weeks or months. Patients with NCGS require regular reassessment for gluten tolerance allowing with time the reintroduction of increasing amounts of gluten.

Introduction

Gastrointestinal (GI) disorders related to gluten or wheat ingestion are becoming increasingly diagnosed. At least three distinct disorders related to gluten exposure are recognized: celiac disease, wheat allergy, and non-celiac gluten sensitivity (NCGS). Diagnostic criteria for celiac disease and wheat allergy are very stringent and several specific disease markers exist, while NCGS lacks a specific biological diagnostic marker. Celiac disease is a life-long autoimmune disease that occurs in genetically susceptible individuals (HLA DQ2 or DQ8) upon the ingestion of gliadin. Pediatricians are well aware of the clinical symptoms (diarrhea, abdominal distension, weight loss and growth failure, as well as extraintestinal signs such as anemia, fatigue, mood alteration, skin involvement, etc.). The diagnostic screen is based on the presence of autoantibodies (anti-endomysium and anti-transglutaminase IgA antibodies) and confirmed by the presence of duodenal villous atrophy with an increased number of intraepithelial lymphocytes [1]. In children with a classical presentation and at least 10-fold elevated autoantibodies, HLA compatible with celiac disease, a duodenal biopsy is no more indispensable before starting a gluten-free diet (GFD) [2]. Similarly, the diagnosis of wheat allergy is relatively clear-cut, and pediatricians, allergologists, and pediatric gastroenterologists easily evoke this diagnosis in a child presenting with allergic GI, skin, or respiratory symptoms usually minutes after the ingestion of wheat or gluten. Specific IgE in conjunction with skin prick and patch tests allow further evoking this diagnosis prior to starting an exclusion diet [3, 4].

At least three distinct disorders related to gluten exposure are recognized: celiac disease, wheat allergy, and NCGS

In contrast to celiac disease and wheat allergy, NCGS is relatively unknown to pediatricians and pediatric specialists. As for celiac disease and wheat allergy, in patients with NCGS, symptoms appear after the ingestion of gluten after a variable interval of few hours up to sometimes several days. Since diagnostic biomarkers are missing, the diagnosis of NCGS can be only suspected once celiac disease and wheat allergy have been formally excluded, since clinical presentations largely overlap. The only reliable diagnostic test that confirms the suspected diagnosis is a double-blind gluten/placebo challenge [5].

The first description of NGCS goes back to the late seventies reporting 8 women with abdominal pain and diarrhea related to the ingestion of gluten, disappearing on GFD, but reappearing upon a gluten challenge [6]. However, only about 30 years later, this entity was fully recognized by gastroenterologists and first reports in children are quite recent and date from 2014 [7]. To improve the diagnostic criteria and to better characterize NCGS, an expert meeting, published as the Salerno Experts' criteria, took place in 2014, defining NCGS as a "syndrome of intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing foods" [8].

Epidemiological Studies on NCGS

Over the last couple of years, GFD became very fashionable and it is estimated that up to 20% of Americans choose to follow a GFD, most often without a medical advice. Thus, GFD is on an exponential rise – due to this new demand, a quickly growing industry offering an increasing panel of gluten-free products parallels this phenomenon. Most often this gluten avoidance is motivated by the observation of "feeling better" on GFD without a medical diagnosis of a gluten-related disorder. Since specific diagnostic markers are missing, the large majority of data on NCGS are based on patients' self-reported gluten-induced symptoms. Several studies tried to estimate the prevalence of NCGS: one of the first reports comes from the Center for Celiac Research at the University of Maryland (USA) reporting a prevalence of gluten avoidance of approximately 6% in a population of patients with GI symptoms seen at a tertiary center [9], while other reports indicate a prevalence of 0.5 up to 10% in a general population [10–13]. All studies show a clear predominance of women. The huge variability of prevalence estimates reflects the fact that these data are based on patient-reported symptoms in relation to gluten consumption excluding patients diagnosed with celiac disease or wheat allergy. Few reports indicate that NCGS is not restricted to adults, but it may also occur in children and adolescents. A recent Sicilian study in 555 high school students (mean age 17 years) indicated a prevalence of self-reported NCGS of 12.2% with the leading symptom irritable bowel syndrome (IBS) [14]. However, less than

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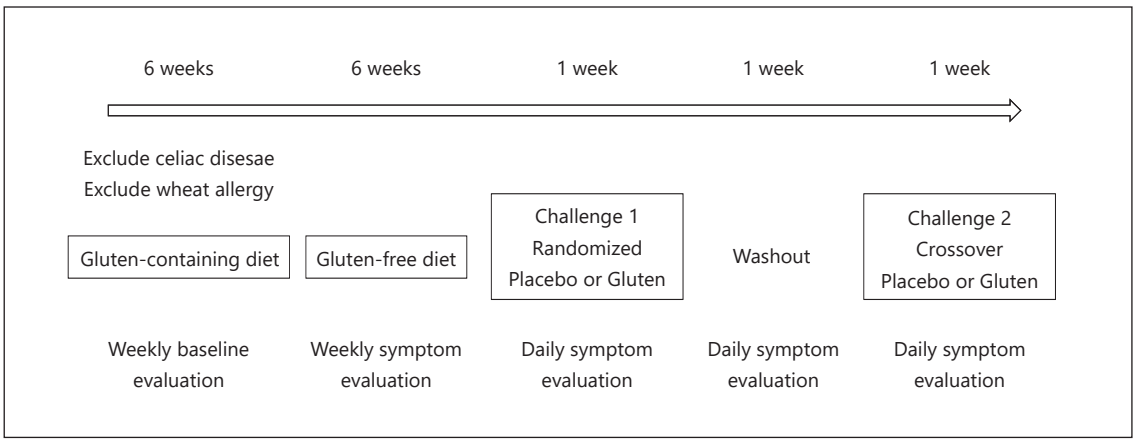

Fig. 1. Suggested algorithm for the diagnosis of non-celiac gluten sensitivity (Salerno Experts' criteria). While on a gluten-containing diet, exclude celiac disease and wheat allergy. Evaluate baseline symptoms (questionnaire) and quantitate one of the three most significant symptoms on a weekly basis. After at least 6 weeks of a gluten-containing diet, switch to a 6-week strict gluten-free diet with weekly evaluation of symptoms. If there is a decrease of symptoms of 30% or more, perform a double-blind crossover challenge with either the sequence "placebo – washout – gluten challenge" or the sequence "gluten challenge – washout – placebo." During these weekly challenges or washout, perform daily symptom evaluation allowing a firm diagnosis of appearance of symptoms caused by gluten ingestion.

a quarter was consulting for medical advice. A markedly lower but still impressive rate (5.2%) of gluten avoidance in children (median age 10.6 years) was reported in a subanalysis of the New Zealand Asthma and Allergy Cohort Study [15]. It is interesting to note that studies based on a double-blind placebo-controlled approach to diagnose NCGS (see below) indicate that more than two-thirds of patients experiencing gluten sensitivity do not react in a reproducible manner to the gluten challenge suggesting that the prevalence of NCGS based on a clear-cut diagnosis is reduced to at least half if not less compared to the numbers reported so far. In comparison, even after correcting the estimates, NCGS seems to be two or three times more prevalent than celiac disease (with an estimated prevalence for celiac disease of 1%).

Clinical Presentation and Diagnosis of NCGS

The clinical presentation of NCGS is variable with multiple intestinal and extraintestinal symptoms occurring within hours, but in some patients only after several days upon the ingestion of gluten. The Salerno Experts' criteria [8] list bloating and abdominal pain as the most frequent GI symptoms, followed by diarrhea, epigastric pain, nausea, and alternating bowel habits or constipation. Some patients also report oral aphthous ulcerations or reflux symptoms evoking gastroesophageal disease. Frequent extraintestinal symptoms are a general lack of wellbeing, headache, tiredness, anxiety, but also muscle and joint pain, skin rash/dermatitis, anemia, numbness or foggy mind are reported. Even less specific symptoms such as sleeping disturbances, mood swings, or hallucinations were reported after gluten ingestion. The great majority of intestinal symptoms overlap with classical celiac disease and even more importantly with either forms of IBS, diarrheal IBS, or IBS with constipation [16]. A small pediatric study on 15 children with gluten sensitivity reported that intestinal symptoms are clearly predominant with abdominal pain as the lead symptom (80%), followed by diarrhea (73%), while extraintestinal symptoms were markedly less frequent [7].

Given the high variability of clinical signs, the precise cause relationship (gluten ingestion provoking clinical symptoms) has to be established in a very distinct manner. Unfortunately, no specific biomarker for NCGS exists. Many markers were tested in the past and there are some reports indicating that anti-gliadin (AGA) IgG antibodies are positive in over 50% of patients with suspected NCGS [17] and AGA IgG tend to become negative under GFD in patients with NCGS [18]. However, it was pointed out that AGA probably develop in a majority of patients with an altered (increased) gut permeability without any disease specificity, thus this finding has to be considered with caution [19]. Other markers tested are in vitro basophil activation test in response to food antigens [20] or the number of eosinophils in the intestinal mu-

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Table 1. Symptom questionnaire for the diagnosis of NCGS [22]

– Abdominal pain or discomfort
– Heartburn
– Acid regurgitation
– Bloating
– Nausea and vomiting
– Borborygmus
– Abdominal distension
– Eructation
– Increased flatus
– Decreased passage of stools
– Increased passage of stools
– Loose stools
– Hard stools
– Urgent need for defecation
– Feeling of incomplete evacuation
– Extraintestinal symptoms
– Dermatitis
– Headache
– Foggy mind
– Fatigue
– Numbness of the limbs
– Joint/muscle pains
– Fainting
– Oral/tongue lesions
– Other (specify)

cosa [21]. However, neither test reached a high level of specificity, making them not usable in a routine clinical setting.

The gold standard and so far the sole diagnostic test allowing the confirmation of true gluten sensitivity causing intestinal and/or extraintestinal symptoms upon gluten ingestion is a double-blind placebo-controlled gluten challenge with crossover, as highlighted in the Salerno criteria [8]. The experts recommend a full diagnostic procedure (Fig. 1): patients on a gluten-containing diet experiencing symptoms after the consumption of gluten are tested for celiac disease or allergic reactions to gluten or wheat. Once celiac disease and wheat allergy are ruled out, patients will be put on a GFD for at least 6 weeks. Most often symptoms disappear very quickly within few days, especially GI symptoms. However, a prolonged GFD is necessary since particularly unspecific symptoms such as fatigue, mood changes, or headache may persist for several weeks after the ingestion of gluten. One challenge consists in how to evaluate the decrease/disappearance of symptoms on GFD and reappearance on gluten challenge: the Salerno criteria suggest the use of a modified Gastrointestinal Symptom Rating Scale (GSRS) [22] (Table 1); while on a normal gluten-containing diet each symptom should be evaluated on a weekly basis starting at week 2 prior to the introduction of a GFD. This baseline evaluation serves as comparator to the weekly evaluation on GFD. To measure on a quantitative level, one of the three main clinical symptoms is assessed numerically using a Numerical Rating Scale (NRS) with a score ranging from 1 (mild) to 10 (severe) [8]. A drop of at least 30% on the NRS for at least 50% of the time is considered as a symptomatic response indicating a likely link between the ingestion of gluten and experienced clinical symptoms. However, the ultimate confirmation of the diagnosis of NCGS requires a double-blind placebo-controlled challenge with crossover. The gluten challenge should be based on a daily intake of at least 8 g of gluten with a defined amylase/trypsin inhibitor (ATI) content (see below) and free of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) over 1 week (in patient with fluctuating symptoms even longer), followed by 1 week washout and a crossover to placebo for another week. It must be assured that the vehicle for the placebo is truly gluten-free. Ideally, patients and physicians are both blinded to the protocol allowing unbiased evaluation. Symptoms are evaluated on a daily basis as above and a variation of at least 30% on gluten challenge versus placebo is considered significant. The arbitrary 30% cutoff has to be validated in the future by independent studies. In daily clinical practice, this diagnostic setting is often not possible, since patients are already on a gluten avoidance diet and not willing to increase their gluten intake for a prolonged period to allow a proper baseline evaluation. Thus, a diagnostic challenge is a pragmatic way to evoke the diagnosis of NCGS. In addition, in routine clinical care a double-blind approach is not very realistic; therefore, most settings propose a single-blinded testing that sometimes needs to be repeated, since many patients are prone to experience strong nocebo effects, complicating the interpretation of the results.

Patients that test negative on a blinded gluten challenge have to be examined for other causes of IBS-like symptoms, especially FODMAP intolerance. The recent report of Skodje et al. [23] clearly highlights the importance of FODMAPs in patients' symptoms. They performed a double-blind crossover challenge in 59 adults with self-reported gluten sensitivity (celiac disease was formally excluded) with a random assignment to receive muesli bars containing placebo, fructan (2.1 g), or gluten (5.7 g) for 7 days. Participants crossed over to each study arm after a minimum 7-day washout period allowing that all 59 individuals completed the three challenges. Based on the GSRS-IBS, 24 participants showed highest scores

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while consuming fructan, 22 on placebo, and only 13 on gluten. This indicates that fructan might be a major trigger for clinical symptoms in patients reporting gluten intolerance. This Norwegian study further extended the findings from a previous study from Peter Gibson's group in Australia [24]: in 37 individuals with self-reported NGCS put on a FODMAP reduction diet prior to a challenge with high gluten (16 g), low gluten (2 g), or placebo, already the FODMAP restriction significantly reduced clinical symptoms. On challenge, all patients reported symptoms that increased with the duration of the challenge independent of the treatment arm: 30% of participants showed symptoms in response to placebo and overall gluten-specific effects were only observed in 8%. The observation of a high nocebo rate complicates the interpretation of these challenges. The recent report on 28 children with presumed NCGS further underlies the difficulty of diagnosis [25]. This first randomized double-blind placebo-controlled crossover trial in children was based on three steps: initially 1,114 children with chronic functional GI symptoms alone or in combination with extraintestinal symptoms were screened for a potential link of symptoms to gluten ingestion. 96.7% did not show any relation of symptoms to gluten-containing food. Finally, only 36 children were included in the study with 5 children improving during the run-in phase (2-week exposure to a gluten-containing diet for baseline evaluation). 31 children had an open GFD over 2 weeks, 3 did not respond, thus only 28 children (mean age 11.4 years) entered into the placebo-controlled crossover trial with a 2-week gluten/placebo challenge, 1-week washout, and another 2-week crossover. Eleven children (39%) showed a gluten-specific response based on a numerical score of the perception of GI symptoms; however, no difference was observed in the severity of the global score comparing challenges with gluten to placebo, in addition no differences were observed between the placebo and gluten-challenged group when analyzing any biological parameters included in this study.

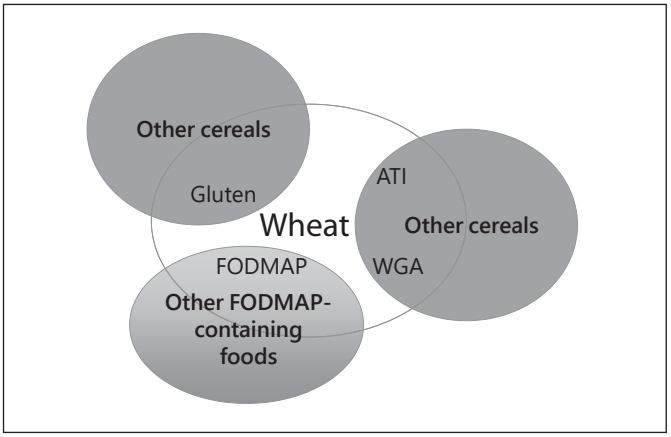

Fig. 2. Non-celiac gluten sensitivity is a syndrome of intestinal and extraintestinal manifestations after the ingestion of gluten. However, the pathophysiology is more complex, since patients report symptoms after the ingestion of wheat, but these are only partially relieved on a gluten-free diet. This might reflect the fact that other components of wheat or other cereals, such as wheat germ agglutinins (WGA), amylase/trypsin inhibitor (ATI), or fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) might trigger the symptoms. Since some components are shared with other nutrients, such as fruits or vegetables (for FODMAP), a more in-depth analysis is necessary for patients still symptomatic on a strict gluten-free diet.

Pathophysiology of NCGS

The diagnostic difficulties and uncertainties, even in specific clinical trials, reflect a potentially more complex pathophysiology of NCGS than previously suspected (Fig. 2). The current notion that clinical symptoms are triggered in response to the ingestion of gluten proteins seems too simplistic. Gluten is a storage protein of wheat, rye, and barley and it accounts approximately for 75% of the total grain protein of the endosperm, the remaining proteins being globulin and albumin. Gluten can be separated into monomeric (gliadins) and polymeric prolamines (glutenines). In patients with celiac disease, several gliadin-derived oligopeptides were identified to elicit a specific humoral immune response, while a N-terminal peptide from alpha-gliadin is supposed to induce innate immune responses in celiac disease patients [1, 26]. So far, no specific gluten peptide was identified to be reproducibly associated with NCGS or to trigger specific symptoms. It is important to underline that wheat contains many other components that might be responsible for the symptoms of patients: ATI, lipopolysaccharides, wheat germ agglutinins (WGA), and FODMAPs.

ATI are protective proteins in several cereals including wheat, rye, and barley. They are part of a plant's defensive system and protect against parasites by inhibiting their amylase or trypsin-like enzymes. ATI are highly packed together with gluten in the endosperm, and ATI content differs markedly between modern bread wheat (very high content) compared to older and less complex wheats (low content). ATI are the major allergen causing baker's asthma [27] and it is well known that ATI trigger innate immune responses via the direct stimulation of Toll-like re-

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ceptor 4, thereby enhancing an inflammatory response. When performing a diagnostic challenge for NCGS, it must be assured that the gluten vehicle also contains ATI at the suggested ratio of 0.3 g ATI/8 g of gluten [8].

WGA are also protective proteins binding to virtually all cell types including other plants and fungi; they are highly packed in the germ of wheat grains. As for ATI, WGA are very resistant to heat and proteolysis. Such as lectins, WGA are considered as anti-nutrients within food. Wheat germs contain the highest WGA concentrations (up to 0.5 g/kg [28]) and in its unprocessed form (i.e., in muesli), a markedly higher WGA activity was found compared to foods containing processed wheat germs. WGA have a high potential to bind to human N-acetlyneuraminic acid expressed on cell surfaces, particularly on the glykocalix of enterocytes and immune cells. Upon binding, WGA induce strong proinflammatory responses [29]. Murine peritoneal macrophages responded with high proinflammatory cytokine secretion to WGA stimulation in vitro (TNF-α, IL-1β, IL-12, and IFN-γ) [30]. Similarly, stimulation of isolated human PBMC with minimal amounts of WGA elicited the release of proinflammatory cytokines [31]. These results indicate that WGA have a high potential to initiate or maintain inflammatory responses. In the intestinal tract, this can lead to a disruption of the intestinal epithelial barrier increasing permeability.

Human in vivo data confirming these inflammatory reactions to WGA ingestion are still lacking; however, antibodies to WGA have been detected in the serum of healthy volunteers [32] and in patients with celiac disease high levels of anti-WGA antibodies were measured.

FODMAPs comprise mono-, di-, and oligosaccharides of fructose (fructans) and galacto-oligosaccharides (GOS) as well as polyols, such as sorbitol, mannitol, and xylitol that are partially, poorly, or not at all digested and thus fermented by the microbiome in the colon leading to gas production and colonic distension responsible for discomfort and pain. FODMAPs play an important role in the pathogenesis of IBS and, as already discussed, apparently also for patients with gluten sensitivity. This is not surprising, since wheat contains variable amounts of fructans depending on the fermentation process. An Australian study analyzed 55 commonly consumed breakfast cereals, breads, pulses, grains, and biscuits indicating significant fructan concentrations even in gluten-free products [33]. Spelt bread had the lowest fructan content in this analysis, helping to understand why patients with IBS tolerate spelt bread better than others.

Treatment Options of NCGS

Once the link between gluten ingestion and clinical symptoms is confirmed, a strict GFD is indicated for several weeks to months. However, wheat contains several other elements (ATI, WGA, FODMAPs) that can trigger symptoms potentially confusing the clinical situation. The reduction to gluten as sole causative food ingredient is too simplistic. As discussed, nutrients other than gluten can maintain the clinical complaints in patients. The best example is fructan, present in wheat, but also in many fruits and vegetables. Therefore, a precise exploration with repeat challenges might help to further improve the clinical situation of a patient feeling some relieve but not completely symptom-free on GFD. There are no clear recommendations for the duration of a GFD, but it is suggested to last for several weeks to months and thereafter reassess gluten tolerance allowing to re-introduce small amounts of gluten. It is important to mention that a GFD alters the microbial homeostasis and a reduction of lactobacilli and bifidobacteria in the gut were observed. Calcium, iron, and folate status have to be monitored on GFD, since some reports indicate a reduced intake on GFD leading potentially to deficiency.

Once the link between gluten ingestion and clinical symptoms is confirmed, a strict GFD is indicated for several weeks to months

It is important to note that the perception of gluten-free food equals healthier food is erroneous. A recent study by Elliott [34] revealed that gluten-free products had a lower sodium level and reduced total fat, but also less protein and a high percentage of sugar-derived calories, comparable to food without a gluten-free claim. Both types of products were considered as of poor nutritional value.

Future Perspectives

There is a major need to improve the diagnostic arsenal for NCGS and if possible to develop clear biomarkers avoiding the quite cumbersome and time-consuming challenge tests. The notion of gluten as the sole trigger of NCGS is too restrictive; recent clinical trials indicate that other food components, such as FODMAPs also play an important role. Thus, future clinical research has to ad-

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dress this point and determine more precisely the role of different foods and nutrients. Since many nutrients contain similar ingredients, the spectrum of different foods associated with NCGS might increase markedly. This is important, since many patients suffer for a long time, while a GFD completely changes their lives; this is not the case for all patients who eventually have other needs. On the other hand, gluten avoidance is becoming more and more fashionable and reflects a certain "healthy" lifestyle, without necessarily indicating a medical need. This trend should be seen with caution particularly for children, since gluten-free products are not necessarily of good nutritional quality, they are quite expensive, and a strict and prolonged GFD might lead to deficiencies. Therefore, clear information for the general population is important to avoid any abuse of restriction diets particularly for children.

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