Eosinophilic gastrointestinal disorders in childhood

Eozynofilowe choroby przewodu pokarmowego u dzieci

Eosinophilic gastrointestinal disorders are a group of chronic inflammatory conditions characterised by the presence of eosinophilic infiltrates in the gastrointestinal wall. These disorders include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis. Their incidence is increasing, with eosinophilic esophagitis known to be the most common form. The etiopathogenesis of eosinophilic gastrointestinal disorders is not fully understood, and most likely associated with an abnormal immune response to food and/or inhalant allergen. They are often accompanied by allergies. Clinical symptoms, especially in the youngest children, are non-specific and depend on the gastrointestinal segment involved. These are most often feeding difficulties and regurgitation in infants, and heartburn, chest pain, dysphagia and food bite impaction in adolescents and adults. Except for eosinophilic esophagitis, there are no uniform diagnostic or therapeutic guidelines for eosinophilic gastrointestinal disorders. Diagnosis is challenging and it is based on the coexistence of clinical, endoscopic and histopathological symptoms and the exclusion of secondary causes of gastrointestinal eosinophilic infiltration. Treatment involves the use of proton pump inhibitors, an elimination diet, or glucocorticoid therapy. Endoscopic or surgical treatment may be necessary in some cases. Clinical remission does not correlate with histopathological remission, therefore monitoring of therapeutic effects requires multiple endoscopies with histopathological assessment of specimens. The aim of this paper was to present the current data on the incidence, diagnosis and treatment of eosinophilic gastrointestinal diseases in children.

Keywords: eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis


Słowa kluczowe: eozynofilowe zapalenie przełyku, eozynofilowe zapalenie żołądka i/lub jelita cienkiego, eozynofilowe zapalenie jelita grubego

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INTRODUCTION

Eosinophilic gastrointestinal disorders (EGID) are rare chronic conditions. These include eosinophilic oesophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC). The prevalence of EGID among children and adults is not fully known and, depending on the research, it is estimated at 2/100,000 for EGE and EC(1) and 4.3–10.7/100,000 for EG, EGE and EC(2). EoE is the most common form (29.5/100,000)(3).

EGID is caused by an abnormal immune response to food or inhalant antigens. Th2 helper cells, interleukin 13 (IL-13) and eotaxin 3 play a role in EoE. Although the pathogenesis of EG is less known, patients have been shown to have higher levels of IL-4 and IL-5, and lower levels of interferon gamma (IFN-γ). Eosinophilic inflammation, coexistence of allergies, peripheral eosinophilia and polysensitisation to food allergens are common clinical features of EoE and EGE(4). The clinical manifestations of EGID are diverse and not very specific. They depend on the part of the gastrointestinal tract involved and the depth of eosinophil infiltration (Tab. 1)(5). Abdominal pain, vomiting, loss of appetite, diarrhoea, and growth disorders are the most common symptoms(6).

So far, except for EoE, no consensus or guidelines on the diagnosis and management of EGID have been established. A triad of chronic or recurrent gastrointestinal symptoms, elevated eosinophil count in endoscopic specimens, and exclusion of other causes of gastrointestinal eosinophilia is needed to establish the diagnosis (Tab. 2)(3,4).

EOSINOPHILIC OESOPHAGITIS

EoE is the most common form of EGID. It is more common in males and patients with atopic dermatitis, inhalant and food allergies(3,6). The most common allergens that trigger symptoms are cow’s milk proteins, wheat, soy and eggs. Clinical manifestations vary with age. These are most often feeding difficulties in infants, vomiting and abdominal pain in young children, as well as dysphagia and food bite impaction in adolescents(7). Attention should be paid to behaviours that enable dealing with oesophageal dysfunction, e.g. longer chewing, keeping food under the cheeks, preference to soft and liquid foods, using large amounts of liquid to wash down the food, difficulty in extending a puree-like diet to solid foods in infants, soaking food in dips, sauces, and liquids(8). There are no specific biochemical markers to diagnose EoE. Peripheral eosinophilia is present in 5–50% of patients. Specific IgEs against inhalant and food allergens are detected in 70% of cases(9). The most common endoscopic findings include circular folds, mucosal rings (trachealisation of the oesophagus), longitudinal furrows, papules, white exudates, no vascular pattern, mucosal congestion and swelling, as well as oesophageal strictures. Normal image of the oesophageal mucosa does not rule out EoE. There are no changes in 10–32% of patients(10). During gastroscopy, it is recommended to collect at least 6 biopsies from 2 segments, most often from the proximal and distal oesophagus(11). It is also advisable to collect gastric and duodenal specimens to exclude other forms of EGID(12). Histopathological eosinophil count of 15 per high power field is indicative of EoE. Additional microscopic abnormalities may include

<table>
<thead>
<tr>
<th>EGID</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>EoE</td>
<td>Vomiting, gastrooesophageal reflux disease, growth impairment, dysphagia, food impaction</td>
</tr>
<tr>
<td>EG</td>
<td>Nausea, vomiting, retrosternal pain, epigastric pain, haematemesis, melaena (with mucosal involvement), gastrointestinal obstruction (with muscle layer involvement)</td>
</tr>
<tr>
<td>EGE</td>
<td>Nausea, vomiting, abdominal pain, diarrhoea, slowed growth/weight loss, intestinal protein leakage or gastrointestinal bleeding (with mucosal involvement), obstruction symptoms, intussusception, perforation (with muscle layer involvement), abdominal distension, ascites (with serous membrane involvement)</td>
</tr>
<tr>
<td>EC</td>
<td>Abdominal pain, tenesmus, diarrhoea with an admixture of mucus and/or blood (with mucosal involvement), torsion of the cecum, intussusception, perforation (with full-thickness involvement)</td>
</tr>
</tbody>
</table>

EC – eosinophilic colitis; EG – eosinophilic gastritis; EGE – eosinophilic gastroenteritis; EGID – eosinophilic gastrointestinal disorders; EoE – eosinophilic oesophagitis.

Tab. 1. Clinical symptoms of eosinophilic gastrointestinal disorders depending on the gastrointestinal segment involved(4).
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Eosinophilic microabscesses, basal zone hyperplasia, fibrosis of the lamina propria, dilated intercellular space, and elongated papillary layer\(^7,11,12\). It should be emphasised that clinical symptoms poorly correlate with microscopic inflammatory changes, and therefore cannot be used in treatment monitoring. Currently, histopathology is the only method that allows to assess the efficacy of EoE treatment.

Differential diagnosis should aim to exclude other diseases associated with oesophageal eosinophilia (Tab. 2).

Untreated EoE is associated with chronic clinical symptoms. Chronic inflammation may in turn result in remodelling and fibrosis of the oesophageal wall, oesophageal strictures, and as a result, swallowing disorders. There is no evidence that EoE can lead to cancer\(^7,12\).

The treatment of EoE aims to achieve clinical and histopathological remission\(^3,7,12\). It involves the use of an elimination diet and pharmacotherapy, i.e. proton pump inhibitors (PPIs) and glucocorticoids (GCS).

Dietary treatment allows for clinical and histopathological remission without pharmacotherapy. However, comorbid atopic diseases may also require the elimination of many foods, and additional dietary restrictions may lead to nutritional deficiencies and reduce patients’ quality of life. Three types of diets are used in dietary treatment: an individual diet based on allergy testing, an empirical diet that eliminates 6 basic allergens, and an elemental diet. A diet based on allergy testing (skin prick and patch tests, specific IgE) was found to be effective in inducing histological remission in about 1/3 of adult patients and about 50% of children. Currently, it is rarely recommended\(^7,13\). Elemental diet, based on amino acid mixtures, allows to achieve histological remission in 90% of adult and paediatric patients\(^7,13\). However, poorly tolerable taste, requiring some patients to introduce enteral nutrition, and the feeling of alienation due to the inability to participate in shared meals, which results in a significant reduction of patients’ quality of life, are its disadvantages. Additionally, the reintroduction of food into the diet requires several endoscopies\(^3,7,13\). The empirical diet eliminates foods that most typically trigger EoE. Elimination of 6 allergens (six-food elimination diet, SFED), such as milk, egg, wheat, peanuts, seafood and soy, allowed for remission in 50–81% of children\(^13\). The elimination of multiple allergens is difficult; therefore, subsequent studies assessed the use of a four-food elimination diet (FFED): milk, wheat, egg and soy. Clinical and histological remission was achieved in 40%

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**Fig. 1. Empirical diet in eosinophilic esophagitis, step-up strategy**\(^{13}\)

- **TFED** (milk, wheat/gluten)
  - Follow-up for remission (clinical symptoms, endoscopy, biopsy)
  - Lack of improvement
  - Improvement
  - Continue the diet, consider introduction of wheat

- **FFED** (milk, wheat/gluten, egg, soy)
  - Follow-up for remission (clinical symptoms, endoscopy, biopsy)
  - Improvement
  - Continue the diet, consider introduction of eggs and soy

- **SFED** (milk, wheat/gluten, egg, soy, nuts, seafood)
  - Follow-up for remission (clinical symptoms, endoscopy, biopsy)
  - Improvement
  - Continue the diet, consider introduction of seafood and nuts

- **Consider other therapeutic methods**

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**Fig. 2. Empirical diet in eosinophilic esophagitis, step-down strategy**\(^{13}\)

- **Empirical diet, SFED or FFED**
  - Follow-up for remission (clinical symptoms, endoscopy, biopsy)
  - Improvement
  - Continue the diet, consider introduction of eggs and soy

- **Consider elemental diet or other therapeutic options**

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**Follow-up for remission**

- Clinical symptoms, endoscopy, biopsy
and 64% of children, respectively\(^{(13)}\). Of the above-mentioned allergens, milk and wheat were the most common triggers of symptoms. The need to repeat gastroscopy to confirm improvement and assess the recurrence of histopathological changes after introducing each food is a disadvantage of all these diets\(^{(3,7,13)}\). According to the step-up strategy, it is recommended to start elimination with a smaller number of products, which, unlike in the step-down strategy, allows to reduce the number of endoscopies to determine the factor that triggers inflammation (Figs. 1, 2)\(^{(13)}\).

According to previous EoE management algorithms, endoscopic improvement after treatment with PPIs ruled out EoE. The concept of oesophageal eosinophilia responding to proton pump inhibitors (proton-pump inhibitor-responsive oesophageal eosinophilia, PPI-REE) is no longer used since 2017\(^{(7)}\). Recent studies have found that PPI therapy reduces inflammation in EoE and effectively induces remission in children and adults\(^{(7,12)}\). Current guidelines recommend PPI therapy as an alternative treatment method\(^{(7)}\). The recommended doses of omeprazole are 1–2 mg/kg/day in 2 divided doses for children, 20–40 mg twice/day for 8 weeks (then the dose should be reduced to the minimum effective dose) for adults. PPIs administered in 2 doses have been shown to be more effective than a single dose\(^{(7)}\). After one year of PPI therapy, histological remission was maintained in approximately 70% of patients with EoE. According to some studies, recurrence of symptoms 3–6 months after treatment discontinuation was observed in most patients. Further observations are needed to support the efficacy and safety of this therapy\(^{(7,13,14)}\).

Swallowed topical corticosteroids allow to achieve clinical and histological remission. Budesonide and fluticasone are most commonly used. The problem is the lack of availability of a suitable form of the drug. Fluticasone in the form of an aerosol is applied directly into the oral cavity without a spacer. Budesonide nebuliser suspension is administered orally. Admixture of sucralose, apple juice or honey produces a viscous syrup consistency,
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Sodium cromoglycate, antihistamines, leukotriene receptor antagonists, omalizumab and infliximab have been used in the treatment of EoE 

Histological examination reveals eosinophilic crypt inflammation and eosinophilic abscesses. The presence of ≥30 eosinophils in ≥5 high-power fields (HPFs) indicates the diagnosis of EG (9). Oral systemic and inhaled GCSs are used in the treatment. An elimination diet allows for clinical and histopathological remission in some patients. The presented data are based on studies in small groups of patients and require further analysis (3,15).

EOSINOPHILIC GASTROENTERITIS

EGE is a rare condition with eosinophilic infiltration involving the stomach and small intestine. The prevalence is 5.1/100,000 (10). The disease is more common in children under the age of 5 years (2). Coexisting allergies are found in 52% of children (2). The most commonly reported symptoms are nausea, vomiting, epigastric pain, rapid satiety, retrosternal pain, epigastriac pain, haematemeses, melena; gastrointestinal tract obstruction may appear with the involvement of the muscle layer (Tab. 1) (3). Laboratory findings may indicate peripheral eosinophilia, hypalbuminaemia, iron deficiency and anaemia.

The endoscopic picture of EG is non-specific and varied. Redness, fragile mucosa, polyps, erosions and ulcerations may occur (3,11). Histological examination reveals eosinophilic mucosal infiltration with eosinophilic crypt inflammation and eosinophilic abscesses. The presence of ≥30 eosinophils in ≥5 high-power fields (HPFs) indicates the diagnosis of EG (9). Oral systemic and inhaled GCSs are used in the treatment. An elimination diet allows for clinical and histopathological remission in some patients. The presented data are based on studies in small groups of patients and require further analysis (3,15).

EOSINOPHILIC GASTRITIS

In the case of EG, clinical symptoms coexist with eosinophilic infiltration of the gastric wall, in the absence of other causes of eosinophilia. The prevalence is 6.3/100,000 (2). The prevalence increases with age, with a predominance in females (2). Coexisting atopic diseases are found in 58.9% of children (2). The clinical symptoms depend on the layer of the gastric wall involved. Inflamed mucosa is associated with nausea, vomiting, rapid satiety, retrosternal pain, epigastric pain, haematemesis, melena; gastrointestinal tract obstruction may appear with the involvement of the muscle layer (Tab. 1) (3). Laboratory findings may indicate peripheral eosinophilia, hypalbuminaemia, iron deficiency and anaemia. The endoscopic picture of EG is non-specific and varied. Redness, fragile mucosa, polyps, erosions and ulcerations may occur (3,11). Histological examination reveals eosinophilic mucosal infiltration with eosinophilic crypt inflammation and eosinophilic abscesses. The presence of ≥30 eosinophils in ≥5 high-power fields (HPFs) indicates the diagnosis of EG (9). Oral systemic and inhaled GCSs are used in the treatment. An elimination diet allows for clinical and histopathological remission in some patients. The presented data are based on studies in small groups of patients and require further analysis (3,15).
clinical and histopathological remission\(^{(3,19)}\). The anti-IL-5 antibody reduced peripheral and tissue eosinophilia, but did not alleviate clinical symptoms. Omalizumab, an anti-IgE monoclonal antibody, reduced clinical symptoms, but had no effects on the histopathological picture. Thiopurines have been shown to be effective in treatment-resistant cases\(^{(20)}\). Surgical treatment should be performed in the case of pyloric or small intestinal stenosis that does not respond to the dietary or pharmacological treatment used\(^{(3,11)}\).

**EOSINOPHILIC COLITIS**

EC is a rare inflammatory disease of the large bowel. The prevalence is 2.1/100,000, and atopic diseases coexist in 52% and 35.9% of paediatric and adult patients, respectively\(^{(21)}\). In infants, EC is often triggered by an allergy to cow’s milk proteins or soy\(^{(11)}\). Clinical symptoms depend on the depth of infiltration. Mucosal involvement causes abdominal pain, tenesmus, diarrhoea with an admixture of mucus and/or blood, whereas full-thickness involvement causes torsion of the caecum, intussusception, and perforation (Tab. 1)\(^{(1)}\). Endoscopy may reveal mucosal granulation, erythema, erosions or ulcers, and exudative lesions. As in the case of EG and EGE, there is no diagnostic consensus on eosinophil count for EC. It is assumed that ≥50 eosinophils per HPF accompanied by clinical symptoms may help reach the diagnosis after excluding other causes of eosinophilia\(^{(20)}\). In infants and young children, an elimination diet is the main therapeutic approach. In older children and adolescents, it may be necessary to introduce GCs (prednisone or budesonide)\(^{(3,11)}\). In the case of relapses or steroid dependence, azathioprine or 6-mercaptopurine should be considered\(^{(3,11)}\).

**CONCLUSION**

Eosinophilic gastrointestinal diseases are rare. The disorders are underdiagnosed due to the lack of characteristic symptoms and diagnostic difficulties. Except for EoE, there are no recommendations on the management in patients with EGID. The presence of clinical symptoms, allergies and elevated histopathological eosinophil counts may help reach the diagnosis. Therapeutic data is based on studies in small groups of patients and requires further analyses.

**Conflict of interest**

The author does not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

**References**