

## Clinical Manifestations and Treatment Response of Eosinophilic Gastrointestinal Diseases in children: A 5-year Study in an Iranian Referral Hospital

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### Abstract

**Background:** Eosinophilic gastrointestinal disorders (EGIDs) are a group of uncommon inflammatory diseases. In this study, we aimed to evaluate the prevalence of EGIDs, clinical manifestation and their response to treatment in a Children Medical Center in Iran.

**Method:** Between 2011 and 2016, all patients, aged <18 years old, who had pathology-confirmed diagnosis of EGIDs and underwent endoscopy in our center, were included in the study. Patient demographics, clinical presentation, laboratory data, radiologic findings, endoscopic findings, histological findings and the results of treatment were retrieved from the participants' medical records.

**Results:** The prevalence of EGIDs in children in the gastrointestinal unit of our hospital during these years was reported as 5 per 1000 children. The most reported clinical symptoms in patients with EoE were nausea (75%), vomiting (69%), and epigastric pain (62.5% each). All of the patients had a hypoallergenic diet. Seventy-five percent of the patients used fluticasone spray. The most frequent symptom in the patients with EoC was rectal bleeding (100%), followed by diarrhea (73%), irritability (23%), and loss of weight gain (18%). All of the patients had a hypoallergenic diet. Twenty-seven percent of the patients used Neocate milk and the use of cetirizine and ketotifen were reported in 18% of patients. EoGE was reported in only two patients (mean age: 10.25 years).

**Conclusion:** During the 5-year period, most cases of EGIDs were related to EoC and EoE, and all cases improved in response to treatment. The hypoallergenic diet was identified as a common effective treatment for the studied patients.

**Key Words:** Eosinophilic colitis, Eosinophilic esophagitis, Eosinophilic gastritis, Eosinophilic gastroenteritis, Eosinophilic gastrointestinal disorders.

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## 1- INTRODUCTION

Eosinophilic gastrointestinal disorders (EGIDs) are a group of uncommon inflammatory conditions characterized by focal or diffuse eosinophilic infiltration of the bowel wall (1, 2). The disorders, based on the location of the pathological eosinophilic infiltration, are classified as eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic gastroenteritis (EoGE) and eosinophilic colitis (EoC) (3). There are numerous clinical manifestations associated with this disease which range from conditions requiring surgery to relieving discomfort over long periods (4-7). Mostly, in EoG and EoC patients, the most common symptoms of mucosal involvement are abdominal pain, diarrhea, bloating, nausea and vomiting (8). Severe EoGE might come with protein losing enteropathy, hypoalbuminemia, anemia, malabsorption and weight loss. Children and adolescents may experience growth retardation, failure to thrive, and postponed puberty. Patients with muscular involvement might develop intestinal obstruction or sub-obstruction, as a result of mechanical and functional blockage due to the eosinophilic inflammation of the muscular layer (9). The serosal form is described by the eosinophilic infiltrate of all layers of the bowel wall which might appear along with eosinophilic-rich ascites, bloating and abdominal pain (10-12). Although histopathology is the gold standard for diagnosis, recognition of imaging features of this rare disorder helps early diagnosis and therapy (1).

The use of dietary and corticosteroids as the first-line treatments is recommended through the evidence from case reports and small uncontrolled case series (13-16). In this study, we aimed to evaluate the prevalence of EGIDs, clinical findings and their response to treatment in a Children Medical Center in Iran.

## 2- MATERIALS AND METHODS

This cross-sectional study was carried out in the referral hospital of Children's Medical Center, the most experienced and sub-specialized hospital for pediatrics, Tehran, Iran between 2011 and 2016. This research was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1395.1843).

All patients, aged <18 years old, who had pathology-confirmed diagnosis of EGIDs and underwent endoscopy in our center, were included in the study. The patients' demographic information, clinical presentation, laboratory data, radiologic findings, endoscopic findings, histological findings and the results of treatment were retrieved from the participants' medical records.

According to the pathological records, at least two pieces of tissues were taken, by an experienced endoscopist, from a single abnormality location with a standard forceps, and multilevel biopsies were defined as specimens obtained from the proximal (10 cm above the squamocolumnar junction) and distal ends of the esophagus. The specimens were fixed in formalin, embedded in paraffin and then stained with hematoxylin and eosin (HE) for pathological diagnosis. The numbers of eosinophils in the squamous epithelium were counted (17).

Diagnoses of EGIDs were confirmed histologically by a pathologist and were defined as: EoE, esophageal eosinophilia with  $\geq 15$  eosinophils (eos) per high-power field (hpf) (18, 19); EoG, gastric mucosal eosinophilia with  $\geq 30$  eos/hpf in at least 5 hpfs (20); and EoC, colonic mucosal eosinophilia with  $\geq 50$  eos/hpf (19, 21).

### 2-1. Data analysis

Statistical analyses were implemented using SPSS (Statistical Package for the Social Sciences) version 13.0 software

(SPSS Inc.). All categorical variables were described as frequency rates and percentages. Normally and non-normally distributed data were presented as mean  $\pm$  SD and medians (25th percentile and 75th percentile). Two-sided  $\chi^2$ -tests were used to compare the differences between groups.

### 3- RESULTS

During a 5-year period (October 2011 to October 2016), 64 cases of EGIDs were recruited in the study. After excluding 24 patients (22 cases due to lack of pathological information and 4 cases due to diagnosis of IBD), 40 patients were included in the study. The frequency of

EGIDs among the patients was as follows: 22 cases of EoC, 16 cases of EoE, and 2 cases of EoGE. No cases of EoG were reported in this study. In the two years of 2013-2014 and 2015-2016, the largest number of patients (10, 25%) was recognized among the recruited children.

In general, the prevalence of EGIDs among the children referred to the gastrointestinal unit of our hospital during these years was reported as 5 per 1000 children (**Table 1**). Whereas, the prevalence of EoC, EoE and EoGE were 0.003, 0.002, and 0.0003, respectively. Except for the first year, no cases of EoG were reported in subsequent years.

**Table-1:** The prevalence of EGIDs in children referred to the gastrointestinal unit of the children medical center

Variable	N	EGID	EoC	EoE	EoGE
2011-2012	1551	0.004	0.002	0.0006	0.001
2012-2013	1538	0.006	0.003	0.003	0
2013-2014	1535	0.007	0.004	0.003	0
2014-2015	1308	0.004	0.002	0.002	0
2015-2016	1493	0.007	0.003	0.003	0
Total	7425	0.005	0.003	0.002	0.0003

EGIDs: Eosinophilic gastrointestinal disorders

EoC: eosinophilic colitis

EoE: eosinophilic esophagitis

EoGE: eosinophilic gastroenteritis

The characteristics of the EoC and EoE patients studied (age, sex, clinical symptoms and treatment performed) are given in **Tables 2** and **3**. The most frequent symptom in patients with EoC was rectal bleeding (100%), followed by diarrhea (73%), irritability (23%), and loss of weight gain (18%). All of the patients had a hypoallergenic diet. The hypoallergenic diet in the treatment of these patients mainly included the removal of the following nutrients from the diet: cow's milk, soy, eggs, nuts, fish and oysters, although oysters were not part of the normal diet of any of the patients

before the onset of the disease. A number of patients adjusted their dietary restrictions in the follow-up treatment based on a skin prick test (SPT). Twenty-seven percent of the patients used Neocate milk and the use of cetirizine and ketotifen were reported in 18% of the patients. All of the patients with EoC responded to the treatment and fully recovered.

The most reported clinical symptoms in patients with EoE were nausea (75%), vomiting (69%), and epigastric pain (62.5% each). All of the patients had a hypoallergenic diet. Seventy-five percent of patients used fluticasone spray. Eighty-

seven percent of patients with EoE fully recovered in response to treatment and 13% had partial recovery. Patients who had hospitalizations even in later years were considered as having a partial improvement. EoGE was reported in only two patients (mean age: 10.25 years). Both of these patients were male; and none of

them had a positive family history. The type of treatment was a hypoallergenic diet and prednisolone for both, and one of them received azathioprine as well. Both recovered completely in response to treatment. Ascites, vomiting, colic pain, hypertrophic pyloric stenosis, and diarrhea were seen in 50 percent of the patients.

**Table-2:** Characteristics of the patients with EoC

Variables		N (%)
Age	Median (IQR)	1.7 (0.7-9.3)
Sex	Male	11 (50%)
	Female	11 (50%)
Clinical manifestations	Rectal bleeding	22 (100%)
	Diarrhea	16 (73%)
	Increased mucus	3 (14%)
	Increase the frequency of bowel movements	1 (4/5%)
	Streaks of mucus	10 (45%)
	Irritability	5 (23%)
	Anemia	1 (4/5%)
	Loss of weight gain	4 (18%)
	Restlessness	2 (9%)
	Stomach ache	1 (4.5%)
Treatment	Hypoallergenic diet	22 (100%)
	Neocate milk	6 (27%)
	Cetirizine	4 (18%)
	Ketotifen	4 (18%)

**Table-3:** Characteristics of the patients with EoE

Variables		N (%)
Age	Median (IQR)	4.8 (3.1-7)
Sex	Male	9 (56%)
	Female	7 (44%)
Clinical manifestations	Cough	1 (6%)
	Nausea	12 (75%)
	Regurgitation	3 (19%)
	Epigastric pain	10 (62.5%)
	Globus	7 (44%)
	Loss of appetite	4 (25%)
	Growth failure	1 (6%)
	Dysphagia	6 (37.5%)
	Vomiting	11 (69%)
	Treatment	Hypoallergenic diet
Fluticasone nasal spray		12 (75%)
Budesonide		1 (6%)

The mean percentage of peripheral blood eosinophils in our patients was as follows: 4.6 in patients with EoC (median=1.7 (0.7-9.3)), 3 in patients with EoE (median=1.3 (0.4-3.2)), and 12.8 in patients with EoGE.

#### 4- DISCUSSION

The present study described 40 children with EGIDs over a five-year period. The prevalence of EGIDs in our hospital during these years was reported to be 5 per 1000 children. The exact incidence of EGIDs is still indistinct. The first description of eosinophilic gastroenteritis was described in 1937 (22), and more than 400 cases have been reported in case reports, case series or retrospective studies (7, 23). Jensen et al. estimated the prevalences of EoG, EoGE, and EoC as 6.3/100,000, 8.4/100,000, and 3.3/100,000, respectively (24). The prevalence of EoG was higher among children <5 years of age, while it was more common among older age groups. In our study, no case of EoG was observed. This might be due to the fact that younger children were referred to this center.

EGIDs symptoms are heterogeneous, depending on the localization and the layer of the gastrointestinal wall involved (Klein's classification). In the study by Shi et al. (17), the prevalence of EOE was 0.34%. Dysphagia was seen in 33.3% and abdominal pain in 25% of cases. In our study, the most common symptom among EoE cases was nausea, followed by patients complaining of epigastric pain (62.5%), which the latter was consistent with the data reported by Hasosah et al. (25). Also, dysphagia was present in 37.5% of patients, which is marginally higher than the percentage reported by Shi et al. (17). Clinical manifestations based on the age of the patients studied might probably explain it. Dysphagia is the most common symptom reported in EOE in Asia and the West. Food entrapment was reported in less than 5% of Asian EOE cases, which is less than the reports from

Western countries (26). Diarrhea, rectal bleeding, and increased mucus production are typical symptoms seen in patients with EoC which mostly occur in infancy and the other group in adolescence and early adulthood (8). In our study, 100% of patients with EoC had rectal bleeding. Diarrhea was reported in 73% of patients. Other symptoms include irritability, poor weight gain, increased mucus, and restlessness, increased frequency of bowel movements, mucus streaks, anemia, and abdominal pain.

Inhaled corticosteroid therapy, diet, and proton pump inhibitor (PPI) are generally used to treat EOE (27). In our study, 100% of patients with EOE had a hypoallergenic diet. And seventy-five percent of the patients used fluticasone spray. Eighty-seven percent of the patients had complete recovery and 13% had partial recovery. In a systematic review by Kinoshita et al. (28), all symptomatic patients with EOE were successfully treated with inhaled corticosteroid therapy and proton pump inhibitors or diets, and a small number of patients required subsequent therapeutic intervention. Kelly et al. showed that a diet based on amino acids (corn, apple, and clear fluids were preferred) completely eliminated clinical symptoms in 8 out of 10 children with EoE (29).

Corticosteroid therapy is the main treatment for EoGE, which is effective for 80% of patients (30). In our study, the patients with EoGE were treated with a hypoallergenic diet, prednisolone and azathioprine. A patient with EoGE with a manifestation of ascites was treated with a hypoallergenic and prednisolone regimen and another one with a manifestation of duodenal obstruction was treated with a hypoallergenic regimen with prednisolone and azathioprine. There are no randomized trials to treat EoGE. Systemic corticosteroid therapy with 20-40 mg per day of prednisone for 2-6 weeks is the most common treatment. In some cases,

continuing treatment with topical budesonide could be helpful (31-33).

Peripheral blood eosinophilia is another association with patients suffering from EGIDs. According to our study, the mean peripheral blood eosinophil in patients with EoE was 3%, in EoC was 4.6% and in EoGE was 12.8%, which was not significant except in EoGE. Although there are some investigations assessing eosinophil levels in the gastrointestinal tract, there are no strict cut-points for the number of eosinophils in the stomach, small intestine, and colon in the EGIDs, and there are no published guidelines as of yet for the diagnosis of these non-EoE EGIDs.

## 5- CONCLUSION

The prevalence of EGIDs among children referred to the gastrointestinal unit of our hospital during the 5-year period was reported as 5 per 1000 children. Most cases of EGIDs were related to EoC and EoE, and all cases improved in response to the treatment. The hypoallergenic diet was identified as a common effective treatment for the studied patients.

## 6- CONFLICT OF INTEREST

None.

## 7- ACKNOWLEDGEMENTS

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