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Eosinophilic gastrointestinal disorders and allergen immunotherapy: lights and shadows.

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37 **Abstract**

38 Allergic diseases, such as IgE-mediated food allergy, asthma and allergic rhinitis, are
39 relevant health problems worldwide and show an increasing prevalence. Therapies for food
40 allergies are food avoidance and the prompt administration of intramuscular epinephrine in
41 anaphylaxis occurring after accidental exposure. However, allergen immunotherapy (AIT) is being
42 investigated as a new potential tool for treating severe food allergies. Effective oral
43 immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) induce desensitization and restore
44 immune tolerance to the causal allergen. While immediate side effects are well known, the long-
45 term effects of food AIT are still underestimated. In this regard, eosinophilic gastrointestinal
46 disorders (EGIDs), mainly eosinophilic esophagitis, have been reported as putative complications
47 of OIT for food-allergy and sublingual immunotherapy (SLIT) for allergic asthma and rhinitis.
48 Fortunately, these complications are usually reversible and the patient recovers after AIT
49 discontinuation.

50 This review summarizes current knowledge on the possible causative link between
51 eosinophilic gastrointestinal disorders and AIT, highlighting recent evidence and controversies.

52
53 **Keywords:** eosinophilic gastrointestinal disorders (EGIDs), eosinophilic esophagitis (EoE), food
54 allergy (FA), oral immunotherapy (OIT), sublingual immunotherapy (SLIT), allergen
55 immunotherapy (AIT).

56 Introduction

57 Eosinophilic esophagitis (EoE), the most studied eosinophilic gastrointestinal disorder
58 (EGID), is a chronic antigen-mediated disease which affects people of any age.¹ The eosinophilic
59 inflammation leads to a progressive esophageal dysfunction, characterized by feeding and
60 swallowing issues and recurrent vomiting in children. In contrast, dysphagia and food bolus
61 impaction prevail in adolescent and adult patients.¹ The diagnosis of EoE requires 1) chronic
62 symptoms, 2) suggestive endoscopic findings, such as esophageal rings, furrows, edema, stricture,
63 narrowing and crepe-paper mucosa, 3) more than 15 eosinophils/high-power field (HPF) in
64 esophageal biopsy specimens, 4) the exclusion of other causes of esophageal eosinophilia.^{2, 3} The
65 overall prevalence of EoE has considerably increased in the last few decades and is currently
66 estimated to be 0.5-1/1,000 subjects.^{4,5} However, EoE is detected in 2.4% - 6.6% of patients
67 undergoing endoscopy for any gastrointestinal (GI) indication, and in about 50%, of patients
68 showing food bolus impaction.⁵ EoE is a multifactorial disorder which results from the
69 combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors
70 and allergen sensitization. All these factors lead to the type 2 inflammation of the esophagus.⁶
71 Non-esophageal EGIDs are uncommon inflammatory diseases caused by allergic and possibly
72 autoimmune inflammation, which affects the GI tract distally to the esophagus. The diagnostic
73 work-up of these conditions requires ruling out other causes of intestinal eosinophilia.^{7, 8} Based on
74 the GI tract involved, non-esophageal EGIDs can be distinguished in eosinophilic gastritis (EoG),
75 gastroenteritis (EoGE) and colitis (EoC). Unlikely EoE, non-esophageal EGIDs currently
76 represent a clinical enigma for clinicians, and standardized guidelines for their diagnosis and
77 treatment are still lacking.⁸

78 IgE-mediated food allergy is a global health issue, affecting from 2% to 8% of the US
79 population and increasing in prevalence.⁹ The classical therapeutical approaches for food allergy
80 include allergen avoidance and the prompt administration of intramuscular epinephrine in case of
81 anaphylaxis. However, food avoidance significantly impacts the allergic patients' quality of life,
82 mainly due to the fear of experiencing severe symptoms; moreover, life-threatening accidental
83 exposure to the causal allergen limits its efficacy. In this context, oral allergen immunotherapy
84 (AIT), such as the administration *per os* of the culprit allergen (oral immunotherapy), is being
85 investigated as a new potential tool for treating severe food allergies. In January 2020, the oral
86 immunotherapy (OIT) treatment for peanut allergy received approval from the U.S. Food and

Drug Administration (FDA). Although the desensitization schedules vary according to the individual Centers' clinical experience, the OIT is generally based on an initial rapid dose escalation phase followed by a buildup phase lasting several weeks or months in order to reach the maintenance dose.¹⁰⁻¹² The aim of the OIT is the achievement of a temporary state (immune tolerance) in which the patient can safely assume a specific amount of the culprit food allergen without life-threatening reactions (desensitization).¹⁰⁻¹² To maintain the desensitization state, patients should continue consuming the tolerated final dose of the food allergen regularly. Mild-moderate side effects typically occur during the administration and escalation of the initial doses and usually require no treatment or antihistamine.¹⁰⁻¹² The medium- and long-term complications of OIT are still unknown and little studied. However, food OIT has been suggested as one of the possible risk factors of EGIDs, mostly EoE; namely, 2.7% of patients who have received OIT for food allergy developed esophageal inflammation.^{6, 13}

Both subcutaneous AIT (SCIT) and sublingual (SLIT) has emerged as an effective and safe alternative treatment in patients with allergic rhinitis and well-controlled asthma and has been shown to modify the underlying cause of these diseases with long-term benefits.¹⁴ To date, the connection between SLIT for allergic rhinitis and asthma and the subsequent development of EGIDs was described in a few case reports.^{15, 16}

A scoping review of articles was performed via the online database PubMed, combining the terms "allergen immunotherapy" AND "eosinophilic gastrointestinal disorders" OR "allergen immunotherapy" AND "eosinophilic esophagitis". The review of literature was performed in October 2020, including the publication years 1990–2020. All studies that met the following criteria were included: 1) case reports, clinical trials, cross-sectional and cohort studies published in English in peer-reviewed journals, 2) participants were children and adult patients with a diagnosis of EGIDs histologically confirmed. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded (Figure 1).

Oral Immunotherapy and EGIDs. The chicken or egg: which came first?

The first case of EoE during OIT for peanut allergy was reported by Hofmann et al. in 2009 (Table 1).¹⁷ Among 28 children enrolled in the US study, one patient developed EoE and

116 achieved disease remission after discontinuing peanut OIT.¹⁷ Two years later, Ridolo et al.
117 described the first Italian case of an 11-year-old boy who developed dysphagia for solid foods and
118 dyspepsia five months after completing the OIT protocol and recovered after an egg-free diet and
119 oral steroid therapy.¹⁸ A large retrospective study of 110 Spanish children undergoing milk OIT
120 reported three cases of EoE that recovered after a complete milk-free diet combined with proton
121 pump inhibitors (PPI) and swallowed corticosteroids.¹⁹ A randomized clinical trial comparing the
122 efficacy of the OIT and elimination diet for egg allergy showed that in the OIT group, one
123 developed EoE and stopped the immunotherapy.²⁰ The first Portuguese case report concerned a 3-
124 year-old girl who developed EoE during milk OIT and recovered after the OIT discontinuation
125 and administration of swallowed corticosteroids.²¹ Semancik and Sayej described three pediatric
126 cases of EoE during peanut OIT.²² Those children presented gastrointestinal symptoms a few
127 weeks after the beginning of the peanut OIT, with clinical improvement after OIT
128 discontinuation.²² A prospective Spanish study of 128 children undergoing milk and egg OIT
129 reported eight cases of EGID.²³ Six patients with EoE developed vomiting and dysphagia, and two
130 children with EoGE presented severe gastrointestinal symptoms and diarrhea.²³ A cohort study of
131 18 children undergoing OIT for milk allergy reported the first Iranian case of EoE in a 3-year-old
132 girl.²⁴ In a case series of 57 Spanish children undergoing milk OIT, EoE was diagnosed in 3
133 patients, who achieved remission after OIT discontinuation.²⁵ A recent prospective study of 90
134 children who underwent egg OIT reported EoE in three patients.²⁶ OIT discontinuation was not
135 effective and patients were successfully treated with a milk-free diet and swallowed
136 corticosteroids.²⁶ Finally, in a large retrospective US study of 783 patients aged 3.5 to 48.3 years
137 who were treated with peanut OIT, only nine patients developed EoE during the buildup and
138 maintenance phase.²⁷

139 EoE is a disease characterized by symptoms related to esophageal dysfunction and
140 eosinophilic inflammation.²⁸ Although esophageal symptoms are required for the diagnosis of
141 EoE, they may not accurately reflect endoscopic and/or histologic findings, and possible
142 inconsistency between clinical and pathological findings has been observed.²⁹ During the
143 desensitization schedule, immediate and delayed GI symptoms are commonly reported, while the
144 diagnosis of EoE, endoscopically confirmed, only occurs in 5.3% of OIT patients.¹⁶ GI symptoms
145 associated with peripheral eosinophilia were described as adverse responses to OIT for different
146 foods in 8% up to 14% of children and have been defined as OIT-induced gastrointestinal and

eosinophilic responses (OITIGER). In addition to the most known immediate IgE-mediated reactions, recurrent non-IgE mediated GI symptoms, mostly vomiting, during the OIT individualized regimen have been reported 2-6 hours after the oral dose administration.³⁰⁻³² OITIGER symptoms appear in the first 2-3 months of OIT treatment and are reversible or transient in most children, modifying the protocol with an individualized and slower dosing regimen.³¹ Although OITIGER patients may develop EoE, most of them can continue the desensitization protocol with complete remission of the GI symptoms without requiring further endoscopies. Patients and their parents were generally reluctant to perform GI endoscopies, because the reduction or discontinuation of dosing improves the symptoms, and children do not show dysphagia or food impaction. Evaluation at baseline, during symptom flares, and in the remission phase should be performed to fully characterize this clinical entity and its possible pathogenetic relationship with EoE.

Although EoE is a possible long-term complication in about 3% of patients undergoing OIT for food allergies,¹³ a preexisting esophageal eosinophilia was recently found before the beginning of the desensitization in adults with IgE-mediated peanut allergy.³³ Moreover, a recent randomized placebo-controlled trial (clinicaltrials.gov no: NCT02103270) reported esophageal eosinophilia in most patients who underwent peanut OIT at week 52, that resolved at the end of the maintaining phase.³⁴

Despite different etiological mechanisms, IgE-mediated food allergy and eosinophilic GI disorders are strongly related.³⁵ Patients with IgE-mediated food allergy have a significantly increased risk (118 times) of developing EoE subsequently in their life, as a late manifestation of the atopic march.^{36, 37} On the contrary, it has been proposed that after a period of a food elimination diet, patients with EoE might develop IgE-mediated hypersensitivity when the food is reintroduced.³⁸ Interestingly, a common pathogenic mechanism between EoE and food allergy is the intestinal epithelial barrier disruption.³⁹ Eosinophils are multifunctional cells that generally colonize the GI tracts, with the exception of the esophagus.⁴⁰ Also, intestinal eosinophils are involved in pivotal homeostatic functions and play essential regulatory roles in epithelial barrier maintenance through mucus and IgA production, tissue repair and remodeling.⁴¹⁻⁴³ In addition to EGIDs, several chronic diseases can be characterized by increased GI eosinophils, such as inflammatory bowel disease, celiac disease, malignancy, vasculitis and connective tissue

disorders.⁸ It is still unclear if esophageal or intestinal eosinophilia might eventually progress to EoE or non-esophageal EGIDs without OIT or whether or not the chronic exposure to the food allergen might increase the preexisting eosinophilic inflammation.

The immunological effects of OIT are complex and concern changes in cytokine responses (switch on the IL-10 pathway), reduced levels of allergen-specific IgE, increased levels of allergen-specific IgG4 and regulatory T-cells and the downregulation of the type 2 inflammation.²⁴ The increase of food-specific IgG4 and its subsequent deposition in the esophagus was the most studied mechanism of EoE pathophysiology during OIT.⁴⁴ The immune complexes are produced when the patient is exposed to high amounts of relevant antigens, as is likely the case in EoE because of local barrier dysfunction.⁴⁴ Whether or not these immune complexes further bind food allergens or other antigens or decrease inducing disease remission is currently unknown. Moreover, IL-10, released by tissue eosinophils, might play a central role in driving IgG4 class-switch.⁴⁴ In the setting of chronic antigen stimulation situations, such as those occurring in allergic epithelial barrier diseases and conditions characterized by impaired gastrointestinal mucosa, levels of IL-10 and IgG4 tend to be high.⁴⁴ Otherwise, IgG4 could represent an epiphenomenon linked to the immune response that leads to the esophageal inflammation.⁴⁴ Therefore, the pathogenetic role of IgG4 in EoE is still controversial and requires further research.

No studies have assessed the rate of non-esophageal EGIDs in children and adults undergoing the OIT for food allergy. To date, only anecdotal case reports have been described. The pathogenesis of non-esophageal EGIDs is still unknown. However, non-esophageal EGIDs can be considered a type 2 inflammatory disease, driven by allergen exposure that leads to the pathological eosinophilic intestinal inflammation.^{8, 45} Indeed, empirical elimination and elemental diets effectively improve GI symptoms and intestinal inflammation, suggesting that exposure to food allergens might be the possible trigger in most affected patients.^{8, 45} A significant group of patients with non-esophageal EGIDs shows a history of concomitant allergic diseases, including IgE-mediated food allergy.⁴⁶ In this context, the initial treatment of non-esophageal EGIDs is usually the dietary approach, but oral corticosteroids have been reported as a second therapeutical choice.^{8, 45}

205

206 **The controversial relationship between aeroallergens and EGIDs**

207 The first report of EGIDs following SLIT was described in 2013 by Miehle et al.⁴⁷ A 44-
208 year-old woman with asthma and allergic rhinitis, developed EoE during SLIT for birch, hazelnut
209 and alder allergies (Table 2).⁴⁷ Clinical manifestations and histological findings resolved four
210 weeks after the discontinuation of SLIT.⁴⁷ In another similar report, Antico and Fante described a
211 23-year-old female who developed heartburn, retrosternal pain and dysphagia four weeks after the
212 initiation of SLIT for dust mite and grass allergies.⁴⁸ The esophageal biopsy confirmed the
213 diagnosis of EoE, and symptoms resolved after the cessation of SLIT.⁴⁸ A 10-year-old girl with
214 asthma and allergic rhinitis developed severe GI symptoms (vomiting and retrosternal chest
215 discomfort) and weight loss six weeks after the beginning of SLIT for dust mites allergy.⁴⁹ Upper
216 endoscopy and histological findings were suggestive of EoE.⁴⁹ After discontinuation of the SLIT,
217 the patient achieved a complete resolution of symptoms and esophageal inflammation.⁴⁹ More
218 recently, Wells et al. described a case of a 10-year-old boy with a previous diagnosis of EoE, who
219 developed a new disease flare after only one week of grass pollen SLIT for allergic rhinitis and
220 well-controlled asthma.⁵⁰

221 The real incidence rate of EoE following SLIT is still underestimated.⁵¹ However, in the
222 US, contraindications for SLIT also include a history of EoE. SLIT may induce EoE with the same
223 pathogenetic mechanism of OIT that is related to the chronic antigenic exposure in patients with a
224 robust allergic susceptibility. While attenuating the IgE-mediated immune reactions, the
225 progressive entrance of the culprit allergen might induce a chronic stimulation of the immune
226 system with the consequent activation of tissue eosinophils and Foxp3-expressing T-cells, and the
227 release of cytokines, such as IL-10, IL-5.^{24, 47, 49, 52, 53} Although most EoE patients achieve disease
228 remission with a food elimination diet, the lack of an adequate diet response in a significant
229 number of subjects may suggest that aeroallergens other than food antigens can play a pathogenic
230 role.^{54, 55} Aeroallergens can trigger and exacerbate EoE; in fact, the SLIT discontinuation
231 improves esophageal inflammation.^{47-50, 56-59} Several single-center studies have evaluated the
232 seasonality and the potential role of aeroallergens in EoE development and reactivation.⁶⁰⁻⁶²
233 Cohort studies reported that children and adolescents with EoE might develop exacerbations in
234 esophageal inflammation during the pollen season depending on the specific aeroallergens to
235 which they are sensitized.^{63, 64} However, patients' follow-up data are not available, rendering the

236 real cause-effect mechanism inconsistent. Furthermore, the association between EoE relapse and
237 season is still controversial, and available results were contradictory.^{6, 65-70}

238 Moreover, the latency between the inflammatory effects of ingested allergens and the
239 appearance of GI symptoms can be exceptionally variable. Whether SLIT is the real trigger of
240 EoE or whether asymptomatic eosinophilic inflammation is already present before the
241 desensitization protocol is still unknown. Also, no clinical trials have currently assessed a latent
242 esophageal inflammation in patients before the beginning of SLIT for allergic rhinitis and well-
243 controlled asthma.

244

245 **EPIT a new potential tool to treat EoE**

246 The cornerstone of pediatric EoE therapy is the off-label use of oral topical steroids and the
247 elimination of the culprit antigen(s) from the diet. Swallowed steroids are generally effective in
248 inducing EoE remission in 53-95% of patients.¹ However, patients may develop new EoE flares
249 when the therapy is suspended. No data on the long-term safety of swallowed steroids is currently
250 available. Potential growth retardation, bone demineralization and adrenal suppression have been
251 reported as potential side effects of swallowed steroid treatment.¹ Food elimination diets are
252 equally effective and are generally based on avoidance of the most common food allergens (milk,
253 wheat, soy, egg, fish and shellfish, nuts) or the prescription of an exclusive elemental formula. The
254 compliance to the elemental diet is significantly impaired by taste, restricted meal variety and lack
255 of insurance coverage.⁷¹ Furthermore, restrictive diets may compromise the patients' growth and
256 nutritional status, lead to nutritional deficiencies and decrease patients' quality of life.⁷¹

257 Epicutaneous immunotherapy (EPIT) is an experimental immunotherapy based on a low
258 dose of allergen exposure through the skin to induce desensitization and reduce cell activation in
259 response to food antigens. In animal models of EGIDs, the EPIT treatment for peanut allergy
260 effectively prevented intestinal inflammation due to chronic exposure to peanuts.^{72, 73} The EPIT
261 protocol has been successfully used to desensitize children with cow's milk and peanut IgE-
262 mediated food allergies.⁷⁴ Recently, EPIT was proposed as a new treatment of EoE, showing
263 exciting and encouraging results in children.⁷⁵ In a phase 2 double-blind controlled trial, Spergel et

264 al. reported that EPIT for milk allergy was safe and reduced esophageal inflammation (< 15
265 eos/HPF) in 47% of EoE enrolled children.⁷⁵ The same research group recently reported that
266 children could tolerate milk without developing GI symptoms two years after the discontinuation
267 of the EPIT protocol.⁷⁶ These data suggest that EPIT may also be safe and effective in treating
268 non-IgE mediated food diseases, and its immunological effects may be sustained and persistent.

269

270 Conclusion

271 The prevalence of IgE-mediated allergic diseases is increasing worldwide. These
272 conditions significantly impact the patients' and their caregivers' quality of life. To date, AIT is
273 the only treatment that could modify the natural history of allergic diseases, favoring the transition
274 from the immediate IgE-mediated disease mechanism to immune tolerance. Current evidence
275 suggests that EoE could be a complication of OIT or SLIT for food and respiratory allergies,
276 respectively. Non-esophageal EGIDs are currently reported as an infrequent side effect of OIT.
277 However, available data are insufficient to demonstrate AIT's causative role in the development of
278 EGIDs.

279 The specific phase (dose escalation or maintenance therapy) of OIT or SLIT in which
280 patients become at the highest risk for EGIDs development needs to be defined. It is still unknown
281 whether EoE has been previously developed or is a consequence of the prolonged allergen
282 exposure during the maintenance phase or if it eventually resolves.¹⁵ Providers should be aware of
283 the risk of developing EGIDs, mostly during OIT. When recurrent gastrointestinal symptoms are
284 observed during food AIT or SLIT, the diagnosis of EGIDs should be promptly considered, and
285 patients should undergo GI endoscopy or less invasive diagnostic tools, such as the esophageal
286 string test.^{77, 78} Fortunately, these complications seem to be reversible by early diagnosis and
287 cessation of OIT and SLIT. However, a strict and prolonged follow-up of the patients undergoing
288 OIT is recommended to detect possible long-term adverse events.

289 Three possible hypotheses could explain the occurrence of EGIDs during OIT and should
290 be investigated: 1) the subclinical eosinophilic inflammation might exist before the desensitization
291 procedure; 2) EGIDs might develop regardless of OIT; 3) OIT might induce EGIDs.³¹ Further

292 studies are required in order to assess the natural history and the specific management options of
293 EGIDs in patients who previously underwent AIT.

294 **Authors contribution**

295 MV and MDF searched the literature and drafted the manuscript, GC reviewed the draft, all
296 authors discussed the review. All authors approved the final version of the manuscript and agreed
297 to be accountable for all aspects of the work.

298 **Key message**

299 Allergen immunotherapy has proven to be an effective treatment for IgE-mediated diseases,
300 including food allergy, allergic rhinitis and asthma. Eosinophilic gastrointestinal disorders are rare
301 disorders that might complicate oral and - in anecdotal cases - sublingual immunotherapy
302 protocols. However, significant esophageal eosinophilia has been reported in allergic patients prior
303 to the beginning of oral immunotherapy. According to the current state of knowledge, clinicians
304 should always consider the risk of EGIDs in patients treated with allergen immunotherapy and
305 promptly perform diagnostic tests, in order to rule out these conditions.

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Table 1. Articles reporting clinical cases of EGIDs development during oral immunotherapy for IgE-mediated food allergy.

Author and year	Country	Sample size	Patients with EGIDs	Age (years)	Sex	Allergen	Way to administer AIT	Duration of OIT treatment	Symptoms	Diagnosis of EGIDs*	Intervention	Outcome
Afinogenova et al., 2020 ²⁷	USA	783	9	n.a.	n.a.	Peanut	OIT	n.a.	n.a.	EoE	n.a.	n.a.
García-Rodríguez et al., 2020 ²⁶	Spain	90	3	n.a.	n.a.	Egg	OIT	2.5-4.5 years	n.a.	EoE	Egg-free diet	Egg was not the culprit food. Patients achieved remission with milk-free diet and swallowed corticosteroids
Yee et al., 2019 ⁷⁹	USA	13	1	8	M	Peanut	OIT	50 months	Vomiting and dysphagia	EoE	OIT discontinuation	Initial disease remission.
Bushyhead et al., 2019 ⁸⁰	USA	1	1	34	F	Peanut	OIT	3 months	Dysphagia to solids	EoE	OIT was stopped, and	Disease remission

											patient started viscous budesonide	
Gómez Torrijos et al., 2017 ²⁵	Spain	57	3	n.a.	n.a.	Milk	OIT	3 years	Dysphagia to solids and chest pain	EoE	OIT discontinuation and milk-free diet	Disease remission
García Rodríguez et al., 2017 ⁸¹	Spain	1	1	55	F	Egg	OIT	3 years	Dysphagia and heartburn upon eating any food	EoE	OIT discontinuation and PPI	Disease remission
Babaie et al., 2017 ²⁴	Iran	18	1	3	F	Milk	OIT	n.a.	Recurrent abdominal pain.	EoE	OIT discontinuation	n.a.
Burk et al., 2017 ⁷⁰	USA	13	2	17 - 18	F and M	Peanut	OIT	8 months and 1.5 years	Dysphagia and heartburn. One patient had weight loss	EoE	OIT discontinuation	Disease remission. After a period of disease remission, one patient

												experienced EoE relapse and started swallowed corticosteroids
Echeverría-Zudaire et al., 2016 ²³	Spain	128	8	3-14	M > F	Milk and Egg	OIT	15-48 months	Abdominal pain, vomiting and dysphagia. The two patients with EoGE experienced more intense symptoms, with diarrhea	EoE was diagnosed in 6 patients; 2 had EoGE	In 3 patients OIT was discontinued. The other 5 patients were treated with PPIs and swallowed steroids without OIT discontinuation	Histological remission in 7 patients
Semancik and Sayej,	USA	3	3	6-11	M	Peanut	OIT	2 weeks	Emesis and dysphagia	EoE	OIT discontinuation	Disease remission.

2016 ²²											and PPI therapy.	
Morais Silva et al., 2014 ²¹	Portugal	1	1	3 years and 9 months	F	Milk	OIT	6 weeks	Emesis	EoE	Topical swallowed fluticasone and a milk-free diet.	Disease remission.
Fuentes-Aparicio et al., 2013 ²⁰	Spain	40	1	7	n.a.	Egg	OIT	6 weeks	Abdominal pain, vomiting	EoE	OIT discontinuation.	n.a.
Sanchez-Garcia et al., 2012 ¹⁹	Spain	110	3	3-14	M	Milk	OIT	29 - 39 weeks	Retrosternal pain and dysphagia	EoE	PPI, oral fluticasone and OIT discontinuation.	Disease remission
Ridolo et al., 2011 ¹⁸	Italy	1	1	11	M	Egg	OIT	5 months	Dysphagia for solid food and dyspepsia	EoE	Egg-free diet and 3 months of oral steroid therapy	Disease remission
Hofmann et al., 2009 ¹⁷	USA	28	1	n.a.	n.a.	Peanut	OIT	n.a.	n.a.	EoE	OIT discontinuation	Disease remission

*All EGIDs diagnoses were performed with upper and lower endoscopy with biopsy.

EoGE, Eosinophilic Gastroenteritis; EoE, Eosinophilic Esophagitis; OIT, Oral Immunotherapy; PPI, Proton Pump Inhibitor.

Table 2. Articles reporting clinical cases of EoE development during sublingual immunotherapy for allergic rhinitis and asthma.

Author and year	Country	Sample size	Patients with EGIDs	Age (years)	Sex	Allergen	Way to administer AIT	Reason to administer AIT	Duration of treatment	Symptoms	Diagnosis of EGIDs*	Intervention	Outcome
Kawashima et al., 2018 ⁵⁷	Japan	1	1	53	F	Japanese cedar pollen	SLIT	Severe allergic rhinitis	13 days	Severe dysphagia and frequent vomiting	EoE	SLIT discontinuation; PPI (20 mg/die)	Histological remission after 8 weeks
Wells et al., 2018 ⁵⁰	UK	1	1	10	M	Grass pollen	SLIT and after SCIT	Allergic rhinitis and well-controlled asthma	1 week	GERD-like symptoms	EoE was diagnosed histologically at age 8	SLIT and SCIT discontinuation. Oral steroid therapy and elemental formula	Clinical improvement
Rokosz et	USA	1	1	9	M	Grass	SLIT	Perennial	17	Complete	EoE	SLIT	Histologi

al., 2017 ⁵⁶						pollen and Dust mite		allergic rhinoconjunctivitis	months	feeding refusal		discontinuation	cal remission
Béné et al., 2016 ⁴⁹	France	1	1	10	F	Dust mites	SLIT	Asthma, allergic rhinitis	6 weeks	Reflux vomiting, retrosternal chest discomfort and weight loss	EoE	SLIT discontinuation; PPI	Histological remission after 12 weeks
Antico and Fante, 2014 ⁴⁸	Italy	1	1	23	F	Dust mites and Grass pollen	SLIT	Allergic rhinoconjunctivitis and asthma	4 weeks	Retrosternal constriction, retrosternal pain and dysphagia	EoE	SLIT discontinuation	Histological remission
Miehlke et al., 2013 ⁴⁷	Germany	1	1	44	F	Hazelnut, Birch,	SLIT	Asthma	4 weeks	Dysphagia	EoE	SLIT discontinuation	Histological

						Alder						ion	remissio n after 4 weeks
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*All EGIDs diagnoses were performed with upper and lower endoscopy with biopsy.

EoE, Eosinophilic Esophagitis; PPI, Proton Pump Inhibitor; SCIT, Subcutaneous Immunotherapy; SLIT, Sublingual Immunotherapy.

Figure legend

Figure 1. Inclusion criteria and search strategy.

