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**Management of eosinophilic esophagitis in children according to atopic status: a retrospective cohort in northeast of France**

Short title: Management of eosinophilic esophagitis in children according to atopy

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**ABSTRACT:**

Introduction: Most children with eosinophilic esophagitis (EoE) are atopic, but the impact of atopy on the remission and development of EoE is still unclear. The aim of our study was to determine the impact of atopy on remission of EoE and to describe allergy tests and the choice of treatment for a cohort of EoE children in France.

Methods: All children diagnosed with EoE between January 2013 and June 2018 in the five pediatric centers in the northeast of France were included. Children were divided into two groups according to personal atopic disorders. Histological remission was defined on the basis of an eosinophilic count below 15 eosinophils per high-power field.

Results: Among the 49 children included, 38 (78%) were atopic. Allergy tests were performed for 45 children (92%). Rates of sensitization were similar in both groups: 64% had food sensitization and 64% had aeroallergen sensitization. The most commonly attempted first-line therapy was with proton pump inhibitors (63%), followed by swallowed topical steroids (STS) (18%). First-line therapy was not associated with atopic status ( $p=0.88$ ). Atopic children had a nonsignificant tendency for a higher remission rate after STS (55% vs. 0%,  $p=0.24$ ) and a higher global remission rate (54% vs. 33%,  $p=0.18$ ) compared with non-atopic children.

Conclusion: Allergy testing is relevant in the majority of children with EoE whether or not they have atopic disorders. Atopy seems to be associated with better response to STS. Further studies are needed to determine whether atopic status determines histological response.

**KEY WORDS:** Eosinophilic esophagitis; children; atopy; remission; sensitization

## 1 **1. Introduction**

2  
3 Eosinophilic esophagitis (EoE) is an emerging disease in pediatrics, with a significant increase  
4 in its incidence and prevalence over the past 10 years. In children, the prevalence of EoE is  
5 estimated to be 111.9 cases per 100,000 inhabitants [1]. EoE is characterized by a chronic  
6 inflammation of the esophagus, which can lead to long-term sequelae of fibrosis and strictures  
7 and decreased quality of life. The diagnostic criteria for EoE were updated in 2018 by  
8 international consensus [2]. EoE is defined by symptoms of esophageal dysfunction associated  
9 with an eosinophilic infiltration into the esophageal epithelium (>15 eosinophils per high-power  
10 field [eos/hpf]), after a comprehensive assessment of non-EoE disorders that could cause or  
11 potentially contribute to esophageal eosinophilia. Management of EoE includes three possible  
12 treatments: proton pump inhibitors (PPI), swallowed topical steroids (STS), or elimination diet  
13 (ED). No comparative study has been performed to define the treatment to be adopted according  
14 to patient characteristics. Therefore, all three treatments can be considered first-line therapies [3,  
15 4].

16 The association between EoE and atopic disorders is now well-established [5]. In a cohort of  
17 449 patients with EoE, 77.5% had at least one atopic comorbidity [6]. The relationship between  
18 EoE and atopy seems to be bidirectional, with each condition increasing the risk for the  
19 subsequent diagnosis of the other. Hill et al. suggested that EoE is a late manifestation of the  
20 atopic march, with a T-helper 2 (Th2) predominant mechanism [7]. Food remains the most  
21 common trigger and ED can achieve remission of EoE for some patients, with variable efficacy  
22 (45.5–90.8%) [8]. In addition, aeroallergens play an important role in the natural course of EoE  
23 by modulating EoE disease activity. Seasonal exacerbation and development of esophageal  
24 eosinophilia were described in murine models exposed to intranasal aeroallergens [9–11].  
25 Moreover, environmental allergen sensitization may decrease the response to therapy [12].  
26 Response to therapy in EoE is heterogeneous, making therapeutic guidelines difficult to  
27 establish. In comparison with asthma, some authors suggest the presence of different phenotypes

28 of EoE, and an atopic EoE phenotype was introduced [13, 14]. A lower rate of remission in the  
29 atopic group than in the non-atopic group was suggested in some studies [15, 16], while Eluri et  
30 al. suggested that food allergy is an independent predictive factor of complete response ( $< 1$   
31 eos/hpf) to STS in adults (OR, 12.95; 95% CI, 2.20–76.15) [17]. There is a lack of information  
32 regarding the impact of atopic history on the natural course and management of EoE, in  
33 particular on treatment efficacy and on the benefit of allergic investigations.

34 The first aim of this study was to compare treatment outcomes in children according to atopic  
35 status. The secondary objective was to describe the use of each treatment (choice of first-line  
36 therapy, implementation) and the results of allergy tests in our patients.

37

## 38 **2. Material and Methods**

39 We performed a multicenter retrospective cohort study between November 2018 and January  
40 2019. Data were collected from five pediatric departments of university hospitals in the  
41 northeast of France: Besançon, Dijon, Nancy, Reims, and Strasbourg. All children aged from 1  
42 to 18 years and diagnosed with EoE between January 2013 and June 2018 were included.  
43 Patients who did not have at least one visit after initiation of treatment were excluded. The  
44 diagnosis of EoE was based on the cut-off value of greater than 15 eos/hpf at 0.25 mm<sup>2</sup> or  
45 greater than 60 eos/hpf at 1 mm<sup>2</sup> in at least one esophageal biopsy specimen during endoscopy  
46 without any other eosinophilic infiltration in the gastric and duodenal biopsies. Data collection  
47 included demographic information, clinical symptoms, personal and family history of atopy,  
48 diagnostic procedures, and response to treatments. Since we used anonymous retrospective data  
49 and since patients are informed of possibilities to retrospectively use their data in each center,  
50 the approval of the Ethics Committee was not needed. The clinical database was declared to the  
51 French Data Protection Authority under number 2214777v0.

52 Patients were divided into two groups: atopic children and non-atopic children. Atopic children  
53 were defined by a personal history of allergic diseases (allergic rhinitis, asthma, atopic

54 dermatitis, and/or food allergy). Atopic sensitization was defined by a positive skin prick test  
55 (SPT) and/or a positive serum specific immunoglobulin E (sIgE) assay. SPT results were  
56 considered positive when the wheal size was equal to or greater than 3 mm from the negative  
57 control papule at 15 min, sIgE results were considered positive at levels greater than 0.35 kU/L  
58 [18], and atopy patch test (APT) results were considered positive if the cutaneous reaction was  
59 greater than or equal to 1+ according to the European Task Force on Atopic Dermatitis.  
60 Causative allergens were defined as those whose elimination from the diet improved symptoms  
61 and histological features on follow-up endoscopies with recurrence upon re-challenge. We  
62 reviewed the effects of therapies on both clinical symptoms and esophageal histology. Primary  
63 outcome was histological response to treatment, defined by an eosinophil peak count below  
64 15 eos/hpf on esophageal biopsy. Secondary outcome was global remission to treatment, defined  
65 as clinical response (subjective complete improvement of symptoms reported by either children  
66 or parents) and/or histological response to treatment.

67

68 Demographics and clinical characteristics are described using mean  $\pm$  standard deviation or  
69 median for continuous variables and frequencies and percentages for categorical variables.  
70 Atopic and non-atopic groups were compared using non-parametric tests: Fisher's exact test for  
71 categorical variables and the Wilcoxon test for continuous variables. A *p* value lower than 0.05  
72 was considered statistically significant. All statistical analyses were performed using the SAS  
73 9.4 software.

74

### 75 **3. Results**

#### 76 *3.1 Study population*

77 A total of 51 patients were diagnosed with EoE in the five pediatric centers between January  
78 2013 and July 2018. Two patients had no follow-up in the designated center after diagnosis and  
79 they were excluded. Among the 49 remaining children, the mean age at diagnosis was 10.3

80 years  $\pm$  4.0 (range: 1.1–15.8) with a majority of boys (84%). Patients had a high incidence of  
81 atopic disorders (38/49 patients, 78%) including: food allergy (51%), asthma (43%), allergic  
82 rhinitis (37%), and atopic dermatitis (26%). Approximately half of the patients (23/49) had at  
83 least one first-degree family member with an atopic condition. No children had siblings with a  
84 diagnosis of EoE. The most common presenting symptoms were food impaction, dysphagia,  
85 abdominal pain, and diet modification (water consumption between each bite, slow meal, food  
86 cut into small pieces, etc). In atopic children, there was a tendency to have more cases of family  
87 history of atopy, more food impaction, gastro-esophageal reflux and vomiting, and fewer cases  
88 of normal endoscopy, but there was no significant difference between atopic and non-atopic  
89 children (Table 1).

90

### 91 3.2 Allergy testing

92 In our cohort, 45 patients (92%) underwent allergy testing: 36 of 38 patients in the atopic group  
93 and nine of 11 patients in the non-atopic group.

#### 94 3.2.1 Type of allergy test

95 In total, 37 patients (75%) had an sIgE assay to foods or/and aeroallergens: cow's milk ( $n=29$ ),  
96 hen's egg ( $n=30$ ), wheat ( $n=29$ ), peanut ( $n=27$ ), treenut ( $n=20$ ), soy ( $n=21$ ), beef ( $n=12$ ),  
97 chicken ( $n=11$ ), veal ( $n=7$ ), house dust mites *Dermatophagoides pteronyssinus* ( $n=11$ ), mold  
98 *Alternaria* ( $n=8$ ), pets ( $n=10$ ), birch pollen ( $n=16$ ), and grass pollen ( $n=13$ ).

99 A total of 35 patients (71%) underwent SPTs including: cow's milk ( $n=24$ ), hen's egg ( $n=26$ ),  
100 wheat ( $n=26$ ), peanut ( $n=23$ ), treenut ( $n=20$ ), soy ( $n=20$ ), beef ( $n=4$ ), chicken ( $n=4$ ), veal ( $n=3$ ),  
101 cod ( $n=21$ ), house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*  
102 ( $n=17$ ), mold *Alternaria* ( $n=15$ ), cockroach ( $n=6$ ), pets ( $n=19$ ), birch pollen ( $n=23$ ), grass pollen  
103 ( $n=25$ ), ash pollen ( $n=11$ ), plantain ( $n=14$ ), mugwort ( $n=12$ ), and latex ( $n=7$ ).

104 APT was undertaken for 19 patients (39%), including: cow's milk ( $n=18$ ), hen's egg ( $n=17$ ),  
105 wheat ( $n=14$ ), peanut ( $n=6$ ), treenut ( $n=4$ ), beef ( $n=12$ ), chicken ( $n=1$ ), veal ( $n=1$ ), and cod

106 ( $n=1$ ). Peripheral blood eosinophil count ( $n=43$ , 88%) was also performed for a majority of  
107 patients, whereas total IgE level was assayed only in one third of the children ( $n=19$ , 39%).

### 108 *3.2.2 Results of allergy tests*

109 Assays for sIgE were positive for more than three quarters of patients and SPT for more than  
110 half in both groups. APT results were positive in 33% and 50% patients, respectively, with and  
111 without an atopic condition. There was no significant difference between the groups (Table 2).  
112 Among patients who underwent allergy testing, 29 of 45 (64%) had a sensitization to at least  
113 one food allergen and 23 of 36 (64%) to at least one aeroallergen. Patients were sensitized to the  
114 following food allergens by at least one of the testing methods: peanut 43%, cow's milk 40%,  
115 hen's egg 40%, wheat 38%, tree nuts 32%, soy 30%, and cod 14%. Other positive test results  
116 were found less frequently: chicken, beef, peas, lupin. Regarding aeroallergens, children were  
117 sensitized to grass pollen 68%, tree pollen 57%, pets 48%, house dust mites 38%, and mold  
118 22%.

119

### 120 *3.3 Treatments*

121 In our cohort, use of PPI therapy and STS was similar among the groups. A majority of patients  
122 received PPI treatment, whether for first-line therapy or during follow-up: 31 (82%) and 9  
123 (82%) patients, respectively, with and without atopic condition. STS were prescribed to 28  
124 (74%) and eight (73%) patients, respectively. By contrast, ED seemed to be used preferentially  
125 for patients with atopic conditions: 22 (58%) versus three (27%), but this difference was not  
126 significant ( $p=1.0$ ). When ED was chosen, ED based on allergy testing was used most  
127 frequently ( $n=16$ ). An empiric ED was prescribed for eight patients: four had a six-food ED, two  
128 had a four-food ED, and two had a two-food ED; only one patient received elemental ED (Table  
129 3). Unfortunately, no causative food was identified. Two patients underwent other therapies: one  
130 had Nissen surgery and one systemic steroid therapy. Esophageal dilatation was performed on  
131 four patients because of esophageal stricture (three had atopic conditions). Regarding first-line



132 therapy, there was no difference between the groups ( $p=0.88$ ). The most commonly attempted  
133 first-line therapies in the whole cohort were PPI (60% and 73%) and STS (18% and 18%) for  
134 atopic and non-atopic groups, respectively. No patient received an ED in first-line therapy.  
135 Combination therapy was used initially for nine patients (Table 4).

136

137

138

### 139 *3.4 Response to treatment*

140 Only three patients did not have esophageal endoscopy for histological evaluation during the  
141 follow-up. After the first-line therapy, 28 patients (57%) underwent histological evaluation, 17  
142 patients (35%) did not undergo histological evaluation but did not achieve clinical remission,  
143 and four patients (8%) had clinical remission but did not undergo any histological evaluation.  
144 Histological evaluation took place after 64% of initiated treatments or changes in treatment.

145 Histological remission was achieved at least once during the follow-up by a higher percentage  
146 of patients in the atopic group (20/37, 54%) than in the non-atopic group (3/9, 33%), but this  
147 was not statistically significant ( $p=0.18$ ). About a quarter of patients had histological remission  
148 after PPI treatment in monotherapy in both groups. Histological and global remission after STS  
149 tended to be more frequent in atopic children: 54% and 64%, respectively, versus 0% and 43%  
150 in non-atopic children. Achievement of histological and global remission after ED was similar  
151 between the groups (Table 5). Seasonal clinical exacerbation was reported in two patients, and  
152 clinical exacerbation after food was reported in four. All of these patients had atopic disorders.

153

## 154 **4. Discussion**

155 We describe the management and outcome of our cohort of 49 children with EoE, according to  
156 atopic status. First-line therapy was not associated with atopic status. The results of allergy tests  
157 were positive in the majority of children in both groups. There is a tendency for atopic patients

158 to have more macroscopic endoscopic anomalies and to have a better chance of remission with  
159 STS.

160 The baseline characteristics of our study population are typical of pediatric EoE patients, and are  
161 similar to those reported in the European Retrospective Pediatric Eosinophilic Esophagitis  
162 Registry (RetroPEER) [19] and in the study by Vigier et al. [20] regarding age at diagnosis,  
163 majority of boys, and prevalence of atopic disorders. There was no difference according to  
164 atopic condition, except for an expected trend for higher prevalence of family atopy in the atopic  
165 group.

166 In our cohort, PPI therapy was used as first-line treatment for 60% of atopic children and 73%  
167 of non-atopic children. This high rate was explained by previous recommendations on the  
168 definition and diagnosis of EoE, including failure of a PPI trial [21–23]. The latest  
169 recommendations published in 2018 suggested that PPI therapy is better classified as a treatment  
170 for EoE than as a diagnostic criterion and the definition of EoE was modified [2, 3]. In our  
171 study, we chose to include all patients with esophageal eosinophilia, even if a PPI trial was not  
172 undertaken or if the patients were PPI-responsive. However, owing to guideline changes during  
173 the period of inclusion, some cases of PPI-responsive EoE may have been considered as peptic  
174 esophagitis before 2018 and not listed in local registries as EoE. This could have led to an  
175 underestimation of the remission rate with PPI.

176 Interestingly, we found a very low rate of ED (58% in the atopic group, 27% in the non-atopic  
177 group, but 0% in first-line therapy) in comparison with the RetroPEER study (82.2% in total)  
178 and the study of Vigier et al. (29.9% in first-line therapy). On the other hand, STS were used  
179 more frequently in our cohort (74% in atopic children and 73% in non-atopic children). One  
180 explanation might be that ED lasting several months may be less acceptable in everyday life for  
181 the child, their pediatrician, and their parents than STS. ED might also be more challenging to  
182 implement because it requires easy access to repeated endoscopy. Contrary to guidelines, allergy  
183 testing-based ED was preferentially used in our cohort. During the period of inclusion, the first

184 assessments of ED based on allergy testing in children were encouraging [24] and this kind of  
185 dietary intervention could be more acceptable for patients. More recently, the step-up empiric  
186 ED appeared to be a better strategy, avoiding endoscopic procedures as well as unnecessary  
187 food restrictions [25].

188 Combination therapy as first-line treatment was used for nine patients. Reasons for this choice  
189 were not explained. As suggested by Munoz-Persy et al., combination therapy generally adds no  
190 benefit but could have a negative impact on the patient's quality of life and it is more difficult to  
191 discern which of the treatments is the most effective [4].

192

193 There was a high rate of histological evaluations in our cohort, since clinical remission was not  
194 confirmed by histological evaluation in only four patients (8%) after first-line therapy.  
195 Endoscopic evaluation was performed after 64% of initial treatments or changes in treatment,  
196 which is higher than reported for a previous cohort (43%) [20]. Moreover, a survey of US  
197 gastroenterologists on the management of EoE found that only 46.3% of the participants  
198 repeated endoscopy with biopsy to monitor EoE [26]. This shows that guidelines on the  
199 necessity of repeated endoscopies to monitor therapy response are now well-known by the  
200 pediatricians in our cohort.

201

202 We found a very low rate of histological remission in comparison with the literature. Although  
203 our remission rate for PPI therapy was 22%, a meta-analysis of 33 studies comprising 619  
204 patients with EoE treated by PPI (of whom 188 children) reported an efficacy of 50.5% for  
205 histological remission.

206 Our histological remission rate after ED was 41%, whatever type of ED was used. In the meta-  
207 analysis of Arias et al. regarding the efficacy of dietary interventions in patients with EoE,  
208 elemental ED was effective in 90.8%, six-food ED in 72.1% ,and ED based on allergy testing in

209 45.5% of cases [8]. Our remission rate is therefore consistent with this meta-analysis since a  
210 majority of patients treated by ED had an allergy-test-driven ED.

211 Our remission rate after STS was lower than that in previous studies: 40% versus approximately  
212 60% [3, 17]. One reason might be the fact that choice of treatment did not follow a structured  
213 study protocol but was left to the discretion of the treating physician. This may have resulted in  
214 inadequate treatment dosing or suboptimal steroid formulation. Furthermore, as some patients  
215 did not undergo histological evaluation, there may be an underestimation of the histological  
216 remission rate. Interestingly, we found a nonsignificant higher remission rate after STS in the  
217 atopic group than in the non-atopic group. This fact was already raised by Eluri et al. [17],  
218 where responders to STS tended to have more atopy (82% vs. 66%;  $p=0.08$ ), and by Shoda et al.  
219 [27], who analyzed EoE endotypes. In our study, the number of children in each group and each  
220 treatment was too small to perform a multivariate analysis and thus we could not determine the  
221 factors associated with remission.

222 There is no consensus on the definition of histological remission and it varies from study to  
223 study. The eosinophil count is commonly used, but the threshold can vary from 1 to 20 eos/hpf.  
224 Sometimes, remission is defined as a 50% decrease in eosinophil count from baseline. In our  
225 cohort, we chose to define histological remission by an eosinophil count lower than 15 eos/hpf.  
226 This choice was made because it is the most frequently used definition in Europe [28].  
227 Moreover, for some of the patients (14/49), the exact number of eos/hpf at diagnosis was  
228 unknown and the count was quantified as greater than 15 eos/hpf.

229  
230 The prevalence of asthma, food allergy, allergic rhinitis, and atopic dermatitis in our EoE  
231 population was 43%, 51%, 37%, and 26%, respectively. In comparison, Capucilli et al. found in  
232 their systematic review a prevalence rate of 27–60%, 24–68%, 57–70%, and 6–46%  
233 ,respectively [5]. The low rate of allergic rhinitis in our population might be due to the  
234 retrospective nature of our study. Symptoms of allergic rhinitis could have been less

235 investigated by the pediatrician than other atopic disorders and therefore under-reported in  
236 medical reports. Our findings regarding the sensitization rates of EoE patients in food and  
237 airborne allergens (64 in both groups) were consistent with published reports in the EoE  
238 pediatric population [12, 19, 29].

239 More interestingly, sensitization rates are similar between atopic children and non-atopic  
240 children, and are higher than the rates in children in the general population [30]. This high rate  
241 of atopic sensitization, regardless of atopic condition, highlights the importance of allergy  
242 testing in children with EoE whether or not they have atopic disorders or a family history of  
243 atopy. Although some studies showed encouraging results regarding ED based on allergy testing  
244 [24], guidelines do not recommend using allergy tests to establish dietary therapy in EoE  
245 patients [3]. We found a higher rate of peanut sensitization (43%) than cow's milk and hen's  
246 egg sensitization (40%), while the most frequently reported causative allergens in children are  
247 cow's milk, egg, and wheat [4, 19, 25]. In the RetroPEER study, patients were sensitized mostly  
248 to cow's milk (45.9%), egg (38.4%), peanut (33%), and wheat (26.5%). Peanut sensitization  
249 seems to be frequent although it is not reported as a causative allergen in children EoE. By  
250 contrast, the role of aeroallergens in the natural course of EoE is prominent (murine models,  
251 seasonal variation of symptoms). Therefore, allergy test could be used to explore a patient's  
252 sensitization and help clinicians to establish EoE phenotypes, rather than to identify causative  
253 foods. More studies are needed to establish the role of allergy testing in EoE patients.

254

255 Owing to the retrospective nature of our study, patient data were limited by the information that  
256 individual providers included in the medical folder. Some patients had multiple sequential or  
257 concomitant therapies, and patient adherence to treatment was not recorded. The remission rate  
258 for each therapy may have been underestimated. As with other studies on EoE management, the  
259 inclusion period extended over 5 years during which there were some important modifications  
260 in EoE recommendations on management and diagnosis. Furthermore, the low number of

261 children included may have decreased the ability to detect differences in remission between the  
262 atopic and non-atopic groups. This may be addressed by compiling a large prospective database  
263 of all children diagnosed with EoE in France. Our study was multicentric, with multiple  
264 physicians in each center and the choice of treatment plan was based on practitioner experience,  
265 preferences, and even changed for the same practitioner over time and according to guidelines.  
266 This may be considered a limitation, but it shows the diverse spectrum of EoE management in  
267 the “real world” and the need for precise guidelines.

268

## 269 **5. Conclusion**

270 Our study describes the management of children with EoE in five French pediatric centers, and  
271 highlights the heterogeneity in the choice of treatments and allergy tests. Allergy testing seems  
272 to be relevant in a majority of children with EoE, whether or not a history of atopy is present. A  
273 prospective study focusing on the benefit of allergy testing, regarding global management and  
274 not only ED, would be helpful to clarify whether allergy tests need to be implemented in the  
275 management of patients with EoE. Our study highlights that atopy might be associated with STS  
276 response. Additional prospective studies are needed to determine whether atopic status  
277 determines histological response, in particular after STS therapy.

278

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## TABLES

Table 1: Baseline characteristics according to atopic status

	All N=49		Atopic children N=38 (78%)		Non-atopic children N=11 (22%)		p**
	N	% / mean(SD)*	N	% / mean(SD)*	N	% / mean(SD)*	
<b>Male</b>	41	84	33	87	8	72.7	0.36
<b>Age at diagnosis (years)</b>	49	10.3 ± 4.0	38	10.1 ± 4.0	11	10.9 ± 4.2	0.61
<b>Family atopic condition</b>	23	47	20	53	3	27	0.18
<b>Presenting symptoms</b>							
Dysphagia	31	63	24	63	7	64	1.0
Abdominal pain	17	35	14	37	3	27	0.73
Food impaction	32	65	27	71	5	45	0.16
Vomiting, nausea	15	31	13	34	2	18	0.46
Reflux	13	26	12	32	1	9	0.25
Diet modification	17	35	12	32	5	45	0.48
Failure to thrive	11	22	9	24	2	18	1.0
Food refusal	4	8	3	8	1	9	1.0
<b>Endoscopic findings</b>							
Normal	5	10	3	8	2	18	0.31
Fixed rings	5	10	4	10	1	9	1.0
Exudates	25	51	19	50	6	54	1.0
Linear furrows	31	63	25	66	6	54	0.50
Edema	5	10	4	10	1	9	1.0
Stricture	6	12	5	13	1	9	1.0
<b>Peak eos/hpf ~</b>	42.1 ± 23.4		43.2 ± 22.8		39.7 ± 25.5		0.66
<b>Increase of serum eosinophil count~</b>	8/43	19	6/33	18	2/10	20	1.0
<b>Increase of total IgE levels~</b>	10/19	53	7/14	50	3/5	60	0.89

\* Percent for qualitative variables, mean ± standard deviation for quantitative variables.

\*\* Fisher's exact test for qualitative variables, Wilcoxon test for quantitative variables.

~ Missing data: Number of eos/hpf ( $n=14$ ), increase in serum eosinophilic count ( $n=6$ ), increase in total IgE levels ( $n=30$ ).

Mean peak eos/hpf: mean peak eosinophils per high-power field.

SD: standard deviation.

Table 2: Atopic sensitizations according to atopic status

	All N=49		Atopic children N=38 (77.6%)		Non-atopic children N=11 (22.4%)		p **
	N	%	N	%	N	%	
<b>Positive specific IgE *~</b>							
Food	28/37	76	22/28	78	6/9	67	1.0
Aeroallergens	13/18	72	10/15	67	3/3	100	0.68
<b>Positive skin prick tests*</b>							
Foods	16/31	52	13/26	50	3/5	60	0.40
Aeroallergens	18/32	57	16/29	55	2/3	67	1.0
<b>Positive atopy patch tests*</b>	7/19	37	5/15	33	2/4	50	0.60

\* Missing data correspond to patients who did not undergo allergy testing: specific IgE levels (food  $n=12$ , aeroallergens  $n=31$ ), skin prick test (food  $n=18$ , aeroallergens  $n=17$ ), atopy patch test ( $n=30$ ).

\*\* Fisher's exact test.

~ Positive specific IgE was defined by a level  $> 0.35$  kU/L; performed by immunoCAP fluorescence enzyme immunoassay.

Table 3: Description of therapies in the cohort according to atopic status

	All N=49		Atopic children N=38 (78%)		Non-atopic children N=11 (22%)		<i>p</i> *
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
<b>PPI therapy</b>	40	82	31	82	9	82	1.0
<b>Swallowed steroids</b>	36	73	28	74	8	73	1.0
<b>Elimination diet (ED)</b>	25	51	22	58	3	27	1.0
Elemental ED	1	2	1	3	0	0	-
Empiric ED	8	16	6	16	2	18	-
Allergy testing based ED	16	33	15	39	1	9	-

PPI: proton pump inhibitors.

\* Fisher's exact test.

Table 4: Choice of first-line therapy according to atopic status

	All N=49		Atopic children N=38 (78%)		Non-atopic children N=11 (22%)		<i>p</i> *
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
<b>PPI therapy</b>	31	63	23	60	8	73	0.88
<b>Swallowed steroids (STS)</b>	9	18	7	18	2	18	
<b>Elimination diet (ED)</b>	0	0	0	0	0	0	
<b>Combination therapy</b>	9	18	8	21	1	9	
PPI + STS	4	8	4	10	0	0	
PPI + ED	2	4	2	5	0	0	
STS + ED	2	4	2	5	0	0	
PPI + STS + ED	1	2	0	0	1	9	

PPI: proton pump inhibitors; STS: swallowed topical steroids.

\* Fisher's exact test.

Table 5: Histological and clinical remission according to atopic status

5a: Histological remission

	All N=49		Atopic children N=38 (78%)		Non-atopic children N=11 (22%)		<i>p</i> *
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
<b>All treatments*</b>	23/46	0.5	20/37	54	3/9	33	0.18
<b>Monotherapy</b>							
PPI ( <i>n</i> =33)**	4/18	22	3/14	21	1/4	25	1.0
STS ( <i>n</i> =29)**	6/15	40	6/11	54	0/4	0	0.24
ED ( <i>n</i> =20)**	7/17	41	7/15	47	1/2	50	1.0
<b>Combination therapy (<i>n</i>=9) *</b>	5/8	62	4/7	57	1/1	100	1.0

5b: Clinical remission

	All N=49		Atopic children N=38 (78%)		Non-atopic children N=11 (22%)		<i>p</i> *
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
<b>All treatments</b>	39/49	80	31/38	82	8/11	73	0.49
<b>Monotherapy</b>							
PPI ( <i>n</i> =33)	10/33	30	7/25	28	3/8	37	0.67
STS ( <i>n</i> =29)	17/29	59	14/22	64	3/7	43	0.40
ED ( <i>n</i> =20)~	10/19	53	9/17	53	1/2	50	1.0
<b>Combination therapy (<i>n</i>=9)</b>	6/9	67	5/8	62	1/1	100	1.0

PPI: proton pump inhibitors, STS: swallowed topical steroids, ED: elimination diet.

\* Fisher's exact test.

\*\* Missing data correspond to patients who did not have histological follow-up: total remission (*n*=3), PPI (*n*=15), STS (*n*=14), ED (*n*=3), treatment association (*n*=1).

~ Missing data correspond to patient lost to follow-up: ED (*n*=1).