Eosinophilic esophagitis in esophageal atresia: Tertiary care experience of a "selective" approach for biopsy sampling

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ABSTRACT

Background: A high prevalence (9.5–30%) of eosinophilic esophagitis (EoE) in patients with esophageal atresia (EA) has been reported. The application of the EoE criteria to EA patients might be problematic. To date, only studies using a “routine” biopsy approach, even in asymptomatic patients, have been performed. The aim of the study was to establish the prevalence of EoE among symptomatic EA patients (EA/EoE group) without anastomotic stricture (AS) and to compare their characteristics with those of EoE patients from general population (EoE group).

Methods: From 2005 to 2018, we reviewed charts of children with EA and EoE. “Selective” biopsy approach only in EA children without AS and/or endoscopic feature of EoE was performed. Characteristics of EA/EoE and EoE groups were compared.

Results: Among 370 EA and 118 EoE, 15 EA/EoE patients were detected (4.0% of EA patients). Male predominance and a high prevalence of allergy without differences between EA/EoE and EoE groups was observed. EA/EoE children were significantly younger (p < 0.0001). PPI-responder patients were significantly more prevalent in EA/EoE group (p = 0.045).

Conclusion: Our data confirm that EA patients are at high risk for developing EoE. High incidence, early onset, and high prevalence of PPI-responders might suggest that esophageal motility disorders interact to increase propensity to EoE in EA patients. However, our study also suggests that overdiagnosis of EoE may occur in EA and that adapted criteria for EoE diagnosis should be developed for EA patients.

Trial registration: Not applicable for this retrospective study.

Keywords: Esophageal eosinophilia, Esophageal dysmotility, Anastomotic stricture
INTRODUCTION

Esophageal atresia (EA) with or without tracheoesophageal fistula is a developmental defect of the upper gastrointestinal tract, representing the most common congenital anomaly of the esophagus. The overall incidence ranges from one in every 2400 to 4500 live births worldwide.\(^1\) Since the first successful surgical repair in 1941, a significant improvement in survival has been reached. Advances in neonatal intensive care, neonatal anesthesia, and surgical techniques have profoundly changed the natural history of EA, limiting mortality to cases with coexistent severe life-threatening anomalies, such as congenital heart disease.\(^2\) Therefore, long-term morbidity and quality-of-life issues have now become priority targets in managing EA patients.\(^3\) Anastomotic stricture (AS) formation, esophageal dysmotility-related conditions, such as gastroesophageal reflux disease (GERD) and dysphagia, as well as respiratory problems, are the most common complications encountered in EA survivors.\(^3\) Furthermore, emerging data suggest that EA patients are more likely to develop eosinophilic esophagitis (EoE) compared to general population.\(^3,4\)

EoE is currently defined as a chronic, immunemediated or antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation that is limited to the esophagus.\(^5\) Recognition of the disease has been increasing over the last 15 years. Current estimated annual incidence is approximately 10/100,000 cases, while prevalence ranges from 10 to 57 cases per 100,000 persons.\(^6\)

Recently, the joint European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines on long-term management of EA suggest excluding EoE in all symptomatic EA patients, especially before proceeding to anti-reflux surgery.\(^3\)

Despite recent attention to the coexistence of EoE in patients with EA, current literature remains limited, as less than 100 cases have been detailed in the literature, with few of those cases from Europe and none from Italy.

The purpose of the present retrospective study was to further examine the relationship between EA and EoE. The primary aim was to establish the prevalence of EoE among surviving patients with EA from Italy and describe their demographic and disease characteristics. The secondary aim was to compare features of EoE in patients with EA (EA/EoE group) with those of patients from general population (EoE group).

METHODS

We conducted a retrospective chart review of children with EA and EoE, from January 2005 to October 2018. Baseline demographics, disease history, and outcome data were analyzed. The authors sent notification of the study to the Ethic Committee (according to the National Guidelines for Observational Study of the Italian Drug Agency, “Agenzia Italiana del Farmaco - AIFA", retrospective studies do not need formal approval by the Ethic Committee and can be initiated by the proposer after notification, using the procedure of silence/consent). Personal data of patients have been collected totally unidentifiably, and patients’ confidentiality was protected.

EA patients

EA patients had surgery at our institution or in other centers. The type of EA was classified according to the Gross classification (A-E classification).\(^7\) The presence of associated anomalies, such as cardiac anomaly or VACTERL (Vertebra, Anorectal, Cardiac, Tracheo-Esophageal, Renal, Limb) association was noted. Long-gap EA (LGEA) was defined as an anatomic distance of ≥3 vertebral bodies between the proximal and distal esophageal segments and was determined according to the hospital protocol.\(^8\) AS was defined as a luminal narrowing at the level of the esophageal anastomosis leading to a functional esophageal impairment and related symptoms.\(^3\) Recurrent and refractory AS were defined according to the ESPGHAN and European Society of Gastrointestinal Endoscopy (ESGE) guidelines on pediatric endoscopy.\(^9\) As per ESPGHAN-NASPHAN guidelines, EA children with symptoms of esophageal dysfunction, such as dysphagia and feeding difficulties, regurgitation and vomiting, food impaction, cough or drooling,
first underwent testing to rule out AS. In case of no evidence of AS, other diagnoses were considered including esophageal dysmotility, gastroesophageal reflux disease (GERD), recurrent tracheoesophageal fistula, tracheomalacia, laryngeal clefts, and EoE. In patients with AS who underwent endoscopic esophageal dilation, biopsy specimens were not routinely collected, unless endoscopic features suggestive of EoE were present (as detailed below). Conversely, routine esophageal biopsy sampling was carried out to rule out EoE in symptomatic patients without AS. EoE diagnosis and treatment were based on current ESPGHAN guidelines (as detailed below). 

**EoE patients**

EoE patients received diagnosis at our institution or elsewhere. All EoE patients were followed-up in the dedicated multidisciplinary eosinophilic gastrointestinal disease clinic, provided with a comprehensive evaluation from a highly experienced team of pediatric gastroenterologists, allergists, and dietitians. According to ESPGHAN guidelines on EoE, diagnosis was made with both clinical and histological features. Symptoms included dysphagia, vomiting, feeding difficulties, abdominal/chest pain, other symptoms suggestive of GERD and food impaction. Multiple biopsies were obtained from distal, mid, and proximal esophagus. At least 15 eosinophils in at least 1 high-power microscopy field (EOS/HPF) were needed for EoE diagnosis. Endoscopic typical features were noted, such as multiple esophageal rings, linear furrows, white plaques, and crêpe-paper mucosa. As per current recommendations, all patients received a trial of 8 weeks of proton pump inhibitors (PPIs) (esomeprazole or lansoprazole 2 mg/kg/day) followed by endoscopic and histological reassessment.

Patients showing clinico-histological response to PPIs were labeled as having PPI-responsive esophageal eosinophilia (PPI-REE). PPI-nonresponsive children underwent dietary treatment (amino acid-based formula or empiric elimination diet) and/or swallowed topical corticosteroids (fluticasone propionate or oral viscous budesonide). Data on personal and family history of allergic disorders were collected, including bronchospasm, allergic rhinitis, eczema, and food allergy. All patients underwent skin prick testing and specific IgE evaluation for both food and inhalant allergens.

### Upper gastrointestinal endoscopy

In all patients, any acid suppression medication was discontinued at least 4 weeks before upper gastrointestinal endoscopy (UGIE). UGIEs were performed under general anesthesia with a pediatric video endoscope (Olympus GIF N180, 

### Table 1. Demographics and EA characteristics in children with EA and EoE (EA/EoE group)

| Abbreviation | EA, esophageal atresia; EoE, eosinophilic esophagitis; VACTERL, Vertebra-Anorectal-Cardiac-Tracheoesophageal-Renal-Limb; CNS, central nervous system; AS, anastomotic stricture. a. According to the Gross classification. b. ≥ 3 vertebral bodies between the proximal and distal esophageal segments. c. According to the ESPGHAN and ESGE definition. |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number of patients | 15 |
| Age at last visit [years; median (range)] | 9.0 (4.8-18) |
| male/female | 10/5 |
| Type of EAa [number (percentage)] |  |
| Type A | 1 (6.6) |
| Type B | 1 (6.6) |
| Type C | 13 (86.6) |
| Type D | 0 (0.0) |
| Type E | 0 (0.0) |
| Long gap EAb [number (percentage)] | 6 (40.0) |
| Associated anomalies [number (percentage)] | 11 (73.3) |
| VACTERL association | 4 (26.6) |
| Heart defect | 4 (26.6) |
| CNS abnormalities | 3 (20.0) |
| Anorectal malformation | 2 (13.3) |
| Pulmonary defect | 1 (6.6) |
| Genitourinary defect | 1 (6.6) |
| History of AS [number (percentage)] | 12 (80) |
| Recurrent/refractory ASc | 5 (33.3) |
| Previous antireflux surgery [number (percentage)] | 5 (33.3) |
| Toupet fundoplication | 3 (20.0) |
| Nissen fundoplication | 2 (13.3) |
XP190 N, XP 160, H180J, H190, Q165; Olympus Medical, Tokyo, Japan).

Statistical analysis

Descriptive statistics were expressed as a median (range), and mean ± standard deviation (SD) for continuous variables and as frequencies (%) for categorical variables. Statistical comparisons between EoE patients from general population (EoE group) and children with EA and EoE (EA/EoE group) were analyzed using Mann Whitney Wilcoxon Test for continuous variables. Fisher exact test and χ² test was used for nominal variables. A p-value of <0.05 was considered significant. Statistical analyses were performed using Prism version 6.0 (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

During the study period, clinical charts of 370 patients with EA and 118 patients with EoE were reviewed. Among these, 15 children with both EA and EoE (EA/EoE group) were identified; therefore, 4.0% of EA patients developed EoE and 12.7% of EoE children had a previous history of EA repair.

All 15 children of the EA/EoE group were in follow-up since birth. The median age at last visit was 9 years (range 4.8–18) and a male predominance (66.6%) was detected. The type C was the most dominant subtype of EA (86.6%). Six children (40.0%) had LGEA (all underwent esophago-esophageal anastomosis). Associated congenital defects were reported in 11 patients (73.3%). History of AS was observed in 12 (80%) patients, 5 of them (33.3%) had recurrent/refractory AS. Five (33.3%) children previously underwent antireflux procedures. Demographics and disease characteristics of EA/EoE children are summarized in Table 1.

Comparison of clinical characteristics between EA/EoE group and EoE patients from general population (EoE group) is illustrated in Table 2. Overall, among all 118 EoE children, male-to-female prevalence ratio was 2.5 with no difference between groups (2.0 vs 2.6 for EA/EoE and EoE group, respectively; p = 0.75). At the time of EoE diagnosis, EA/EoE children were significantly younger than EoE patients from general population (median: 4 vs 10.9 years; p < 0.0001). Peak EOS/HPF did not differ between groups (mean ± standard deviation: 50.1 ± 26 vs 59.8 ± 29 EOS/HPF; p = 0.24). Overall, 66.1% of children had allergies with no difference between groups (53.3 vs 67.9%; p = 0.38). PPI-responder patients were significantly more prevalent in EA/EoE group that in EoE group (66.6% vs 35.9%; p = 0.045). Among the 5 EA/EoE patients who were non-PPI-responders, 2 achieved clinical and histological remission while on dietary treatment (milk free diet) and 3 on swallowed topical corticosteroid.

DISCUSSION

This retrospective series is the first from an Italian cohort to evaluate the coexistence of EA and EoE and confirms that EA patients are at high risk for developing EoE.

| Abbreviation | EA/EoE | EoE | p       |
|--------------|-------|-----|---------|
| Number of patients | 15 | 103 |         |
| Male/female (ratio) | 10/5 (2.0) | 75/28 (2.6) | 0.75a |
| Age at EoE diagnosis [years; median (range)] | 4 (1.1–12.5) | 10.9 (1.7–23.5) | <0.0001b |
| Peak EOS/HPF at diagnosis [number; mean ± SD] | 50.1 ± 26 | 59.8 ± 29 | 0.24b |
| History of allergy [number (percentage)] | 8 (53.3) | 70 (67.9%) | 0.38a |
| PPI-REE [number (percentage)] | 10 (66.6) | 37 (35.9) | 0.045a |

Table 2. Clinical characteristics of EA/EoE and EoE patients. Abbreviation: EA, esophageal atresia; EoE, eosinophilic esophagitis; EOS/HPF, eosinophils per high-power field; PPI-REE, proton pump inhibitor - responsive esophageal eosinophilia; SD, standard deviation. a. Fisher’s exact test. b. Mann Whitney test; bold text indicates a statistically significant difference.
| Year of publication | Study period | Institution (Country) | Total Nr of EA patients | EA/EoE | EoE prevalence | Study design | Patients included |
|---------------------|--------------|-----------------------|-------------------------|--------|----------------|--------------|-------------------|
| Dhaliwal et al.\textsuperscript{11} | 2014 | 1999-2012 | SCH (Australia) | 103 | 18 | 17% | retrospective | All surviving patients who had surgery for EA |
| Krishnan et al.\textsuperscript{12} | 2018 | 2000-2014 | SCH (Australia) | 110 | 20 | 18% | retrospective | # |
| Petit et al.\textsuperscript{13} | 2019 | 2005-2014 | CHU Sainte-Justine (Canada) | 73 | 15 | 21% | prospective | Children born with EA-TEF were prospectively included |
| Lardenois et al.\textsuperscript{14} | 2019 | 2007-2015 | University Hospitals of Lille and Strasbourg (France) | 63 | 6 | 9.5% | prospective | All patients aged 15-20 years with medical history of EA |
| Yasuda et al.\textsuperscript{15} | 2019 | 2016-2018 | Boston Children's Hospital (United States) | 310 | 47 | 15%\textsuperscript{*} | retrospective | Patients with EA who underwent at least one upper endoscopy with biopsies |
| Pesce et al.\textsuperscript{16} | 2019 | 2015-2017 | GOSH (United Kingdom) SCH (Australia) | 63 | 19 | 30% | retrospective | All children with EA referred consecutively either for refractory upper GI symptoms or as part of surveillance program |

\textbf{Table 3.} Details of studies reporting EoE prevalence in EA children. \textit{Abbreviation}: EA, esophageal atresia; EoE, eosinophilic esophagitis; GOSH, Great Ormond Street Hospital; SCH, Sydney Children's Hospital. \#. Non clearly detailed, conceivably as the study by Dhaliwal et al. (similar study periods were analyzed). \* Patients who met histologic criteria of >15 eosinophils/high powered field.
The prevalence of EoE in our cohort of EA survivors (4.0%) was much greater than the 0.1-0.57% estimated in general population, but lower than previously reported (9.5-30%). Characteristics and main results of previous series are summarized in Table 3. Beside possible regional variability, the main factor accounting for this difference is the approach to esophageal biopsy sampling: “routine” versus “selective”. Indeed, we collected biopsies only in symptomatic EA patients without AS and/or with typical endoscopic features of EoE, while other authors performed routine biopsies in all patients, even asymptomatic. It is still not clear whether all EA patients should undergo routine esophageal biopsies to rule out esophageal eosinophilia (EE). Current guidelines on EA recommend, with a low level of evidence, excluding EoE in symptomatic EA patients, especially before anti-reflux surgery. EE does not always mean EoE. Recent international consensus on EoE points out that the presence of EE on histologic examination without further consideration of the clinical presentation is not diagnostic of EoE. Authors also highlight that EoE is ultimately diagnosed after excluding other contributing factors for symptoms and EE. However, the application of the EoE clinical criteria to EA patients is problematic, since esophageal symptoms in EA patients might arise from many different underlying conditions.

Virtually all EA survivors have an impaired esophageal motility, which is the key pathophysiological factor leading to long-term digestive and respiratory morbidity. It is conceivable that esophageal dysmotility in EA patients might play a pivotal causative role also in EoE development, increasing the risk of severe GERD and producing stasis of food and saliva into the esophageal lumen. Prolonged mucosal acid exposure time and retained material into the esophagus might cause itself mucosal injury and esophageal eosinophilic-predominant inflammation. Moreover, esophageal stasis may also result in prolonged exposure to allergens (both aero and food allergens) which facilitates the inflammatory eosinophilic cascade in susceptible patients.

The topic of AS and its relation to EE and EoE deserves a specific point of discussion. AS is the most frequent post-operative complication of EA and must be first excluded in all symptomatic patients. AS may contribute to eosinophil inflammation due to stasis and retained bolus. Therefore, AS treatment by esophageal dilation may interrupt the chain of events leading to mucosal inflammation, by improving both anterograde and retrograde flow through the esophagus. A recently published case report describing the resolution of EE in a patient with achalasia, who underwent pneumatic dilation of the cardia, supports this speculation. On the other hand, patients with EA and EE were described to be at increased risk of recurrent/refractory AS formation, which remains a major challenge in the postoperative management of EA. Although the pathogenesis of recurrent/refractory AS is not fully understood, it is likely that the presence of EE, whether it be EoE or not, might play an important role in stricture formation. Treating EE with topical corticosteroids, by reversing the subepithelial fibrotic process, may possibly result in a reduction of AS recurrence, and subsequent need for further invasive procedures.

In the present study, we also aimed to compare demographic and disease characteristics between EA/EoE children and a large group of EoE patients from general population. Consistent with literature data on EoE, we found a strong male predominance and a high prevalence of atopic comorbidities (allergic rhinitis, asthma, food allergy), without significant differences between groups. Furthermore, no difference in tissue eosinophilia levels (peak EOS/HPF) was observed.

Similarities in gender distribution, atopic background and histopathological findings suggest that common genetic susceptibility factors might underlie EoE development in EA patients. This hypothesis is corroborated by the study of Krishnan et al. demonstrating a similar gene expression pattern between EoE patients with and without EA.

On the other hand, we observed a higher incidence and early onset of EoE in EA patients than in children from general population. Besides the above mentioned implication of the esophageal
dysmotility, these findings might be related to other factors. Early endoscopic surveillance in EA children might enable early diagnosis of EoE.; (2) The majority (if not all) of EA children are exposed to early-life environment factors implicated in EoE pathogenesis such as admission to the neonatal intensive care unit, antibiotic and acid suppressant therapy in infancy, formula-only, or mixed feeding; Genetic association between EA and EoE through mutations in the Forkhead box (FOX) gene has been hypothesized

Interestingly, we observed a significantly higher percentage of PPI-responders in EA/EoE patients than in the EoE group. Different mechanisms have been proposed to explain the PPI response in EoE. By restoring the acid reflux-induced impairment of mucosal integrity, PPIs correct the abnormal mucosal permeability and prevent antigen penetration. Gastric acid-inhibiting effect is likely to have a significant role in resolving EE in EA children because of their considerably higher risk of developing severe GERD with prolonged esophageal acid exposure. PPIs have been shown to also exert anti-inflammatory effects, by inhibiting the production of pro-inflammatory cytokines and adhesion molecules that act as ligands on the eosinophil cell surface. Of course, as for EoE from general population, PPIs have also been shown to be effective in resolving EE in EA children because of their considerably higher risk compared to the considerably higher risks detailed in previous reports. In our view, the “a posteriori” analysis over a long period (13 years) of symptomatic EA children without AS, could represent the most reliable picture of the relationship between EA and “true” EoE.

In summary, our study confirms in our Italian cohort that EA patients are more prone to develop EoE than general population, but it notably estimates a lower risk than previously reported. Established risk factors for EoE, such as male gender and history of atopy, may contribute to EoE development in EA patients as with general population. Our study suggests that adapted criteria for EoE diagnosis should be developed for EA patients. Indeed, while underdiagnosis of EoE may occur if routine biopsies are not obtained in all patients with EA, overdiagnosis may also occur if eosinophilia is present, but symptoms of esophageal dysfunction relate to complications of EA rather than EoE. It should be kept in mind that EoE is a specific chronic condition carrying a significant burden of disease, as it requires intensive monitoring and long-term medications or dietary restrictions. Moreover, the high prevalence of PPI-REE in our EA/EoE population re-emphasizes the importance of a PPI-trial that has been recently removed from the diagnostic algorithm for EoE. Growing evidence indicates that EoE is an umbrella term for conditions that are unified by EE, but that different disease subgroups with various inflammatory esophageal patterns and/or different clinical features exist. Our study supports the concept that EoE in EA represents a specific subtype of EoE and strongly sustains the vision toward tailored treatment strategies according to different EoE phenotypes. Future research should devote more attention to the role of EE, whether it be EoE or not, in EA children, especially in those experiencing recurrent/refractory AS.

Potential competing interests
The authors report no competing interests.

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Ethics information and consent for publication
The Ethic Committee of Bambino Gesù Children’s Hospital was notified of this retrospective observational study (according to the AIFA National Guidelines for Observational Study, retrospective studies do not need formal approval by the Ethic Committee and can be initiated by the proposer after notification, using the procedure of silence/consent).

Author contributions
RT: contributed to study conception and design, contributed to medical record review and database generation, analyzed the results and wrote initial draft of the manuscript; FR: contributed to study conception and design, contributed to medical record review and database generation, contributed to data interpretation; GA: analyzed the results and contribute to writing the initial draft of manuscript. MMa: contributed to medical record review and database generation, contributed to data interpretation; MMc, CR: contributed to the acquisition and interpretation of data. LV: contributed to medical record review and database generation; GF: contributed to data interpretation; LDO: contributed to study conception and design; AGF: contributed to the acquisition and interpretation of data; JEM: analyzed the results and contribute to writing the initial draft of manuscript; PDA: contributed to study conception and design, analyzed the results and wrote initial draft of the manuscript. All authors contributed to critically revising the manuscript, approved the final version of the manuscript and the authorship list and take full responsibility for the manuscript.

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REFERENCES
1. Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology. J Med Genet. 2006;43:545–554.
2. Ijsselstijn H, van Beelen NW, Wijnen RM. Esophageal atresia: long-term morbidity in adolescence and adulthood. Dis Esophagus. 2013;26:417–421.
3. Krishnan U, Mousa H, Dall’Oglio L, et al. ESPGHAN-NASPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with esophageal atresia-tracheoesophageal fistula. J Pediatr Gastroenterol Nutr. 2016;63:550–570.
4. Krishnan U. Eosinophilic esophagitis in children with esophageal atresia. Eur J Pediatr Surg. 2015;25:336–344.
5. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr. 2014;58:107–118.
6. Moawad FJ. Eosinophilic esophagitis: incidence and prevalence. Gastrointest Endosc Clin N Am. 2018;28:15–25.
7. Gross RE. The Surgery of Infancy and Childhood: Its Principles and Techniques. Philadelphia: Saunders Company; 1953.
8. Bagolan P, Valfré L, Morini F, Conforti A. Long-gap esophageal atresia: traction-growth and anastomosis—before and beyond. Dis Esophagus. 2013;26:372–379.
9. Thomson M, Tringali A, Dumontte JM, et al. Paediatric gastrointestinal endoscopy: European society for paediatric Gastroenterology Hepatology and nutrition and European society of gastrointestinal endoscopy guidelines. J Pediatr Gastroenterol Nutr. 2017;64:133–153.
10. Tambucci R, Angelino G, De Angelis P, et al. Anastomotic strictures after esophageal atresia repair: incidence, investigations, and management, including treatment of refractory and recurrent strictures. Front Pediatr. 2017;5:120.
11. Dhalwal J, Tobias V, Sugo E, et al. Eosinophilic esophagitis in children with esophageal atresia. Dis Esophagus. 2014;27:340–347.
12. Krishnan U, Lijuan C, Andrew GJ, Rothenberg ME, Wen T. Analysis of eosinophilic esophagitis in children with repaired congenital esophageal atresia. J Allergy Clin Immunol. 2019;143, 1455–64.e2.
13. Petit LM, Righini F, Ezri J, et al. Prevalence and predictive factors of histopathological complications in children with esophageal atresia. Eur J Pediatr Surg. 2019;29:510–515.
14. Lardenois E, Michaud L, Schneider A, et al. Prevalence of eosinophilic esophagitis in adolescents with esophageal atresia. J Pediatr Gastroenterol Nutr. 2019;69:52–56.
15. Yasuda JL, Clark SJ, Staffa SJ, et al. Esophagitis in pediatric esophageal atresia: acid may not always Be the issue. J Pediatr Gastroenterol Nutr. 2019;69:163–170.
16. Pesce M, Krishnan U, Saliekellis E, et al. Is there a role for pH impedance monitoring in identifying eosinophilic esophagitis in children with esophageal atresia? J Pediatr. 2019;210:134–140.
17. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology. 2018;155:1022–1033. e10.
18. Lemoine C, Aspirot A, Le Henaff G, Pilouquet H, Lévesque D, Faure C. Characterization of esophageal motility following esophageal atresia repair using high-resolution esophageal manometry. J Pediatr Gastroenterol Nutr. 2013;56:609–614.
19. Tambucci R, Thapar N, Saliekellis E, et al. Clinical relevance of esophageal baseline impedance measurement: just an innocent bystander. J Pediatr Gastroenterol Nutr. 2015;60:776–782.
20. Stave Salgado KV, Rocca AM. Eosinophilic esophagitis and esophageal atresia: coincidence or causality? Arch Argent Pediatr. 2018;116:e61-e69.

21. Little AG, Correnti FS, Calleja IJ, et al. Effect of incomplete obstruction on feline esophageal function with a clinical correlation. Surgery. 1986;100:430-436.

22. Kim H, Park H, Choi H, et al. Retention esophagitis as a significant clinical predictor of progression to esophageal cancer in achalasia. Clin Endosc. 2018;51:161-166.

23. Frieling T, Heise J, Kreyosel C, et al. Eosinophilic esophagitis and achalasia - just a coincidence? Z Gastroenterol. 2019;57:151-155.

24. Markowitz JE, Clayton SB. Eosinophilic esophagitis in children and adults. Gastrointest Endosc Clin N Am. 2018;28:59-75.

25. Jensen ET, Kappelman MD, Kim HP, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2013;57:67-71.

26. Jensen ET, Kuhl JT, Martin LJ, Rothenberg ME, Dellon ES. Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141:214-222.

27. Jensen ET, Kuhl JT, Martin LJ, Langefeld CD, Dellon ES, Rothenberg ME. Early-life environmental exposures interact with genetic susceptibility variants in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141:632-637.e5.

28. Gorter RR, Heij HA, van der Voorn JP, Kneepkens CM. Eosinophilic esophagitis after esophageal atresia: is there an association? Case presentation and literature review. J Pediatr Surg. 2012;47:e9-e13.

29. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, Rayo A, Román E. The role of proton pump inhibitors in the management of pediatric eosinophilic esophagitis. Front Pediatr. 2018;6:119.

30. van Rhijn BD, Weijenborg PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2014;12, 1815-23.e2.

31. Rea F, Caldar T, Tambucci R, et al. Eosinophilic esophagitis: is it also a surgical disease? J Pediatr Surg. 2013;48:304-308.

32. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Dig Dis Sci. 2009;54:2312-2317.

33. Cheng E, Zhang X, Wilson KS, et al. JAKSTAT6 pathway inhibitors block eotaxin-3 secretion by epithelial cells and fibroblasts from esophageal eosinophilia patients: promising agents to improve inflammation and prevent fibrosis in EoE. PLoS One. 2016;11, e0157376.

34. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by esophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013;62:824-832.

35. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology. 2018;154, 319-32. e3.

36. Mudde AC, Lexmond WS, Blumberg RS, Nurko S, Fiebiger E. Eosinophilic esophagitis: published evidences for disease subtypes, indications for patient subpopulations, and how to translate patient observations to murine experimental models. World Allergy Organ J. 2016;9:23.