Introduction

Several esophageal disorders occur in the pediatric population. Eosinophilic esophagitis (EoE) is the most common pediatric esophageal inflammatory condition after gastroesophageal reflux disease (GERD). EoE is an eosinophil-predominant inflammatory disease of the esophagus that affects both pediatric and adult populations. Although clinical presentation and endoscopic features of EoE may vary between both populations, similarities do exist. These similarities include the association with atopic conditions, underlining pathogenesis and disease complications. The relationship between GERD and EoE is quite complex and will not be covered in this narrative review. However, longstanding GERD is a known risk factor for the development of Barrett's esophagus (BE) in
both adults and children. BE is associated with development of dysplasia and, if left undiagnosed, may progress to esophageal adenocarcinoma (EAC). The prevalence of EoE is increasing in the pediatric population. On the other hand, both BE and esophageal neoplasms remain extremely rare in children.

Current research of these disease entities is prioritized to understanding disease pathogenesis and progression, new diagnostic modalities, and developing novel therapeutic options. In this narrative review, we will examine the current epidemiology, clinical practices and recent research and their implications on future practices.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tgh-20-223).

**Methods**

We conducted a literature review search on PubMed and MEDLINE using the terms “Pediatric”, “Barrett’s Esophagus” “Eosinophilic esophagitis”, “esophageal adenocarcinoma” and “esophageal cancer” from January 1989 through April 2020.

**Eosinophilic esophagitis**

**Epidemiology and clinical presentation**

EoE involves antigen-mediated eosinophilic inflammation of the esophagus leading to esophageal dysfunction and clinical symptoms (1-5). In the United States, the prevalence of EoE is estimated at 57 per 100,000 with a male predominance of 3:1 (4,6,7). EoE affects all racial and ethnic groups, with increased prevalence in Caucasians (2,3,6).

Age-related differences in the clinical presentation of EoE in children and adults are appreciated (4,8). In younger children, symptoms include emesis, abdominal pain, nausea, reflux, feeding dysfunction, and failure to thrive (4,9). Feeding difficulties may present as dysphagia, food aversion, choking, gagging, or food impaction (10). Solid food dysphagia is the most common presenting symptom in adolescents and adults, and as many as 50% of adults initially present with food impaction (2,4). For this reason, an adolescent or adult with food impaction warrants further diagnostic evaluation for EoE (8). Other symptoms displayed in adults include reflux, chest discomfort, and upper abdominal pain (4,11). Atopic comorbidities, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, are common (70–80%) in pediatric patients with EoE (2,5).

**Diagnosis**

EoE is a clinicopathologic disease, requiring both clinical and histologic findings consistent with the diagnosis. Thus, endoscopic evaluation by esophagogastroduodenoscopy (EGD) with esophageal mucosal biopsies is necessary. Endoscopic features suggestive of EoE include presence of edema, fixed esophageal rings, white exudates, linear longitudinal furrowing, mucosal fragility, and esophageal narrowing (Figure 1) (5,12). In the pediatric EoE population, inflammatory endoscopic features of edema, exudates, and furrowing are more common (4). Features may also be subtle and in some cases, the esophageal mucosa is normal in appearance (4,13). Progressive disease with chronic inflammation can lead to esophageal remodeling, which can lead to fibrostenotic endoscopic features such as rings, strictures, narrowing, and mucosal tears (10-12). On histology, findings of esophageal intraepithelial eosinophilia (≥15 eosinophils/high power field), basal cell hyperplasia, elongation of vascular papillae, intercellular edema (spongiosis), and degranulation of eosinophils are findings consistent with active EoE disease (Figure 2) (2,5,8,10,14-16). Pathologists can also identify subepithelial fibrosis when there is sufficient lamina propria in biopsy specimens (16). Histopathologic changes in EoE can be patchy; therefore multiple biopsies obtained from three levels (i.e., proximal, middle, and distal) of the esophagus are recommended to maximize diagnostic yield of EoE and to detect subepithelial fibrosis (16).

Both the diagnosis and management of EoE are dependent on mucosal biopsy for accurate diagnosis and to assess the response to therapy. Mucosal evaluation is most commonly performed by EGD. Less invasive modalities for monitoring EoE disease activity and response to therapy are being investigated. The Esophageal String Test (EST) is a minimal invasive technique that utilizes the Enterotest string device which is a gelatin capsule containing a nylon string that is swallowed and later withdrawn through the mouth. EST can detect active EoE inflammation by measuring biomarkers such as eotaxin-3 and major basic protein-1 (8,17,18). Luminal concentrations of eosinophil-
associated proteins obtained by EST were found to correlate with esophageal mucosal eosinophilic inflammation (17,18). A prospective, multisite study evaluating 134 subjects (both pediatric and adult) by Ackerman et al. demonstrated that a 1-hour EST accurately distinguishes active vs. inactive EoE in a less invasive and safe manner compared to endoscopic examination with biopsies (18). Unsedated transnasal endoscopy (uTNE) utilizes a small flexible endoscope for sampling esophageal mucosa and can be performed without anesthesia or sedation in select patients. Studies in pediatrics have shown that it is an adequate, well-tolerated, and cost-effective method of mucosal evaluation for monitoring disease activity in EoE (19,20). Currently the suitability of uTNE in pediatrics is an area under investigation by a network of academic pediatric gastroenterology centers. The Cytosponge is an encapsulated compressed mesh sponge attached to a string. Once swallowed and in the stomach, the capsule dissolves and the sponge expands. Upon withdrawing the sponge through the mouth by the attached string, cells are sampled from the esophagus (8,21). Katzka et al. compared the adequacy and diagnostic accuracy of esophageal sample collection by endoscopy versus the Cytosponge in adult patients and found that samples collected by Cytosponge were adequate in evaluating epithelial activity in adult patients with EoE (21).

In contrast to the tests that sample the mucosa, the endoscopic functional luminal imaging probe (EndoFLIP) serves as an additional diagnostic modality that phenotypically characterizes EoE by assessing esophageal distensibility (i.e., ‘stiffness’) through the use of high resolution planimetry during endoscopy (8,22). Distensibility is defined as the measure of the esophageal

Figure 1  Endoscopic features in pediatric EoE. (A) Normal esophagus for comparison. Endoscopic features in pediatric cases with EoE include (B) esophageal mucosal edema with loss of vascular markings, (C) circumferential rings or trachealization, (D) exudates or white plaques, (E) vertical, longitudinal linear furrowing, or (F) crepe paper esophagus with mucosal fragility upon passage of the endoscope. EoE, eosinophilic esophagitis.
The pathogenesis of EoE involves inflammatory infiltrates including eosinophils, T-cells, mast cells, and their chemokines and cytokines, such as interleukin (IL)-4, IL-5 and IL-3. Therapies have been developed to target these specific immune pathways. Dupilumab...
is a human monoclonal antibody against the IL-4 receptor that inhibits IL-4 and IL-13 signaling and is an effective treatment of several allergic and atopic diseases (27). In a 12-week multicenter, randomized, double-blind, parallel group, placebo-controlled Phase 2 study of adult patients with active EoE, dupilumab reduced dysphagia and histological and abnormal endoscopic features of EoE compared with placebo, and was overall a well-tolerated drug (27). Participants enrolled in this study were required to remain on a stabilized diet 6 weeks before screening and throughout completion of the study. Additionally, they were prohibited to utilize concomitant medications for the treatment of EoE, immunotherapies, investigational drugs other than Dupilumab, and could not start PPI therapy unless having been using the medication in the 8 weeks before screening. Mepolizumab and reslizumab are monoclonal antibodies targeting IL-5. Despite a decrease in esophageal tissue eosinophilia with these drugs, symptomatic improvement has been inconsistent. Potential clinical benefit requires additional studies (27,41). Sialic acid binding immunoglobulin-like lectins (Siglecs) are transmembrane protein receptors expressed on eosinophils. AK002, an antibody directed against Siglec 8, causes apoptosis of human eosinophils (39,41). There is an ongoing phase 2/3 randomized, placebo-controlled trial to assess its safety and efficacy in adolescent and adult patients with active EoE (ClinicalTrials.gov. NCT04322708). Participants in this study are excluded if they have used of oral corticosteroids within 8 weeks prior to screening, had a change in dose in PPI therapy of dietary therapy within 4 weeks prior to screening, or used immunosuppressants or immunomodulatory drugs within 12 weeks prior to screening.

**Barrett’s esophagus**

**Epidemiology and clinical presentation**

BE is defined as the presence of metaplastic intestinal-type columnar epithelium that has replaced the normal squamous epithelium lining of the esophagus (42,43). BE predominantly presents in adults, with a prevalence of 1% to 2% of all patients referred for upper endoscopy. BE is seen in approximately 5–15% of patients exhibiting symptoms of gastroesophageal reflux (GER) (44-46). The prevalence of BE in children varies between 0.05% to 4.8%, with a mean age 12.4 years at diagnosis (46,47). The main risk factor in both adults and children is longstanding GER. BE has been identified in children with reflux after a period of 5.3 years (46). Predisposing risk factors for children include tracheoesophageal abnormalities, neurological impairment, chronic lung disease, hiatal hernia, and increased body mass index in patients without underlying conditions (46,47). In adults, additional risk factors include male gender, central obesity, age over 50 years, tobacco usage, Caucasian race, and family history in a first-degree relative (43,45,48).

Since pediatric BE is rare, there is a paucity of data to suggest that pediatric BE portends a worse prognosis compared to adult BE. However, as previously mentioned, studies in adults have indicated that long duration of GERD symptoms are a risk factor for BE (44-46). Furthermore, there are no specific guidelines available for screening or treatment in children with BE. As the prevalence of pediatric BE increases, pediatric guidelines for screening and management will be warranted. Overall, practice guidelines on the diagnosis and management of BE in adults recommend screening in only patients that meet the identified risk factors including men with chronic reflux disease (>5 years) and two or more risk factors (42,43,45). The American College of Gastroenterology (ACG) suggests, in women, to screen those with multiple risk factors (42,45).

**Diagnosis**

The diagnosis of BE requires identification of salmon colored mucosa extending into the esophagus at least 1 cm proximal to the gastroesophageal junction (GEJ) combined with histological confirmation of intestinal metaplasia (IM) exemplified by the presence of goblet cells (Figure 3) (42). Biopsies from four-quadrants at 2 cm intervals should be obtained over the length of the BE segment during endoscopy (43,45). If BE is suspected, at least eight random biopsies from the segment should be obtained in order to maximize the yield of IM on histology (42,49). In the case of short segments (i.e., <3 cm) of suspected BE, at least four biopsies per cm of circumferential BE and one biopsy per cm in tongues of BE should be obtained (42). If BE is suspected, but there is lack of IM on histology, a repeat endoscopy should be considered in 1–2 years (42).

BE is associated with the development of EAC (43). The risk of cancer progression in BE is 0.2–0.5% per year in patients with nondysplastic changes and up to approximately 6% per year in patients with evidence of high-grade dysplasia (42). The goal of endoscopic
surveillance is to detect dysplasia at an earlier stage. The degree of dysplasia (no dysplasia, low grade dysplasia, high grade dysplasia, adenocarcinoma) determines recommendations for surveillance intervals and the need for endoscopic eradication therapy (EET) (42,43,45). Endoscopy is regarded as the gold standard for screening and is optimally performed utilizing high-resolution/high definition white light endoscopy to visualize mucosal detail (42,43,45). Advanced imaging technologies for endoscopic surveillance have been developed in an attempt to improve detection. These include dye-based chromoendoscopy, electronic chromoendoscopy such as narrow-band imaging, volumetric laser endomicroscopy and confocal laser endomicroscopy (43,50).

Less invasive diagnostic methods have been studied in BE, including the uTNE and the Cytosponge Cell Collection Device. uTNE can be considered as an alternative method to conventional upper endoscopy for BE screening with comparable performance characteristics compared to endoscopy (sensitivity 98% and specificity 100%) (42,45,51). The Cytosponge is a well-tolerated device that obtains esophageal tissue samples for testing of protein biomarkers and has a 73% sensitivity and 94% specificity for the diagnosis of BE (42). The EsoCheck Cell Collection Device, a retractable balloon attached to a string that, when swallowed, gathers cell from the distal esophagus that can be used to detect DNA markers of BE (45). Another novel device is the wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS-3D). WATS-3D utilizes a brush to sample layers of the esophageal epithelium. When used in addition to endoscopic forceps biopsy, WATS-3D increased the overall detection of BE in adults (52).

**Treatment and management**

Among patients with BE, symptoms of GER should be managed with use of daily PPI therapy to maximize acid suppression and treat esophagitis, unless symptoms require twice daily dosing for reflux symptom control (42,43,45). Moreover, studies have shown that use of PPI therapy decreased the risk of neoplastic progression in patients with BE (25,53). Long-term exposure (>3 years) of PPI therapy was associated with a lower risk of EAC and/or BE with high grade dysplasia (53). While it has been proposed that long term PPI use can potentially lead to the development of gastric adenocarcinoma or gastric neuroendocrine tumors through mechanisms that promote pan-colonization of *H. pylori* or hypergastrinemia, respectively, current studies have not supported an association of long term PPI use with gastric cancers, neuroendocrine tumors, or premalignant changes (54-57). In a randomized, double blind placebo controlled trial that followed participants over a medium 3-year period, it was found that pantoprazole was not associated with long-term harmful outcomes with the exception of enteric infections (58). Thus, in cases where PPI use is clinically needed, the benefits outweigh the risks. EET plays an important role in the management of BE, dysplasia, and early EAC. Patients with evidence of nodularity or visible abnormalities in the BE segment
should undergo endoscopic mucosal resection (EMR) of the lesion as both a diagnostic and therapeutic maneuver (42,43). Endoscopic ablative therapies are not recommended in patients with nondysplastic BE due to the low risk of progression to EAC (42,43). However, ablative therapies are considered the preferred treatment strategy for patients with confirmed low grade dysplasia or high grade dysplasia (42). Radiofrequency ablation (RFA) is the most commonly used ablative modality, with high rates of complete eradication of intestinal metaplasia (CEIM) and dysplasia (42,44,59). Cryotherapy involves rapid freezing and slow thawing of tissue resulting in cellular injury through the use of various cryogens and can be used in BE refractory to RFA (60). These endoscopic eradication therapies have not been described for the use of BE in pediatric patients.

**Esophageal neoplasms**

**Epidemiology and clinical presentation**

Esophageal neoplasms are extremely rare in children. EAC and esophageal squamous cell carcinoma (ESCC) comprise the majority of childhood esophageal malignant neoplasms, however several benign neoplasms have been reported. Esophageal neoplasms in children are summarized in Table 1 (61-75). Caustic ingestion, tobacco use, and history of esophageal atresia repair are considered risk factors for both EAC and ESCC (61,62). Both EAC and ESCC, found near or at an anastomotic site, are seen as long-term sequela (>30 years) after reconstruction of esophageal atresia (76-78). It is speculated that after repair, long-standing GERD, esophageal stasis, and mucosal damage lead to the development of these malignancies (76). GER and BE are considered risk factors for EAC (61,79). Approximately 60% of pediatric patients with EAC have pre-existing conditions associated with GER, such as hiatal hernia, esophageal atresia repair, and obesity (62). In a case series of fourteen pediatric patients with EAC, 78% of cases were associated with BE, suggesting that, similar to adults, BE is a strong risk factor for the development of EAC (61).

The most common presenting symptoms of esophageal carcinomas and other neoplasms in children are progressive dysphagia and weight loss (Table 1) (61-75). In adults, EAC predominantly develops in the lower one-third of the esophagus. However, in approximately 40% of pediatric EAC cases, the lesion can be found above the distal esophagus (61,63).

**Diagnosis**

Survival is dependent on various factors including disease stage, prompt diagnosis, growth pattern, tumor location, and rate of growth (62,64). Better outcomes for EAC are seen with surveillance endoscopy and early detection of the disease (45). In a study examining adult patients with BE that developed EAC, 49.3% of patients were in BE surveillance programs and diagnosed by endoscopy. These patients were more likely to be diagnosed at an early stage, have longer survival and have lower cancer-related mortality (80).

Pediatric diagnostic and treatment guidelines for esophageal cancer are not well established due to the rarity of esophageal neoplasms in childhood, thus we focus on review of adult literature and studies. In patients with suspected esophageal neoplasms, diagnosis typically combines information from imaging of the thorax, upper endoscopy or other procedural intervention to obtain histology, and a multidisciplinary evaluation by surgery and oncology specialties. Diagnosis is confirmed by histological review of biopsy tissue (61).

**Treatment and management**

Surgical esophagectomy is considered the treatment of choice for submucosal cancers, poorly differentiated cancers, or cancers with a high risk of lymph node metastasis (42,81). Less invasive surgical resection techniques can be considered. In a retrospective study comparing conventional open esophagectomy (OE), minimally invasive esophagectomy (MIE), and Hybrid esophagectomy, there was no significant difference between the three techniques for the outcomes of lymph nodes retrieved, resection margin-positive disease, and tumor recurrence (82).

Other treatment options in adults include adjuvant chemotherapy and EET (81). EET, which includes EMR and endoscopic ablative techniques such as RFA and cryotherapy, has demonstrated safety and efficacy for eradication of IM and disease remission with few adverse effects (59,81,83,84). Early data in adults suggests the use of immunotherapies as possible treatment options for advanced gastrointestinal (GI) cancers, although there are limited approvals to date (85-87). These types of therapeutics include immune checkpoint inhibitors such as ipilimumab (CTLA-4 inhibitors), nivolumab and pembrolizumab (PD-1/PD-L1 inhibitor), and tyrosine kinase inhibitors targeting human epidermal growth factor
<table>
<thead>
<tr>
<th>Type of esophageal neoplasm</th>
<th>Incidence and prognosis</th>
<th>Tumor characteristics</th>
<th>Clinical symptoms</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal adenocarcinoma (EAC)</td>
<td>High frequency of metastasis</td>
<td>32% cases had BE in surrounding areas</td>
<td>Most common is dysphagia (83%)</td>
<td>Resection (total esophagectomy, partial esophagectomy, esophagogastric resection)</td>
<td>(61-63)</td>
</tr>
<tr>
<td></td>
<td>19 pediatric cases reported</td>
<td>Commonly found in the distal esophagus and GEJ</td>
<td>Weight loss (55%), anemia, dehydration, nausea</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male predominance</td>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Esophageal squamous cell carcinoma (ESCC)</td>
<td>23 pediatric cases reported</td>
<td>Occurrence is evenly distributed within esophagus</td>
<td>Most common is dysphagia</td>
<td>Resection (total esophagectomy, partial esophagectomy, partial esophagogastric resection)</td>
<td>(61,62)</td>
</tr>
<tr>
<td></td>
<td>No gender predominance</td>
<td></td>
<td>Weight loss, anemia, dehydration, nausea</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Esophageal sarcomas</td>
<td>0.1–1.5% of all esophageal tumors</td>
<td>Most frequently occur as polypoid intraluminal masses</td>
<td>Most common is dysphagia</td>
<td>Resection (endoscopic resection, esophagectomy with local excision)</td>
<td>(64-66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT/MRI imaging shows enhancing intramural mass</td>
<td>Weight loss, regurgitation, chest discomfort, respiratory distress</td>
<td>Chemotherapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Esophageal leiomyoma</td>
<td>2.6% of cases occurred in children</td>
<td>Predominantly diffuse form (91%) as opposed to localized lesions (9%)</td>
<td>Most common is dysphagia</td>
<td>Resection (esophagogastric resection, esophagectomy, enucleation)</td>
<td>(67,68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dyspnea, vomiting, coughing, retrosternal pain</td>
<td></td>
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<tr>
<td>Granular cell tumor (GCT)</td>
<td>Most cases of esophageal GCT have a benign course</td>
<td>The esophagus is the most common site of GCT in the digestive tract</td>
<td>Most cases are asymptomatic and found incidentally</td>
<td>Resection (EMR, surgical excision)</td>
<td>(69,70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most cases are solitary lesions</td>
<td></td>
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<td></td>
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<td></td>
<td>Cases with tumor size &gt;1–2 cm may report dysphagia</td>
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Table 1 (continued)
<table>
<thead>
<tr>
<th>Type of esophageal neoplasm</th>
<th>Incidence and prognosis</th>
<th>Tumor characteristics</th>
<th>Clinical symptoms</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile myofibroma</td>
<td>Benign neoplasm</td>
<td>One-third of myofibromas are found in the region of the head and neck</td>
<td>1 case presenting as proximal GI obstruction</td>
<td>Surgical resection</td>
<td>(71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occur as solitary, multicentric or multicentric with visceral involvement</td>
<td></td>
<td>Chemotherapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Histologic features: proliferation of fibroblasts, myofibroblasts or both with intravascular growth</td>
<td></td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor (IMT)</td>
<td>Low-grade neoplasm with potential for local invasion</td>
<td>Occurs in soft tissue and viscera, with esophageal location considered rare</td>
<td>Dysphagia, chest pain, globus sensation, emesis, weight loss, cough, fever</td>
<td>Resection (esophagectomy)</td>
<td>(72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 pediatric cases reported</td>
<td></td>
<td></td>
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<tr>
<td>Plexiform fibromyxoma (PF)</td>
<td>Follows a benign course after resection</td>
<td>More commonly occurs in the stomach, with preference for the gastric antrum</td>
<td>–</td>
<td>Resection (local excision, thorascopic resection)</td>
<td>(73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 pediatric case reported</td>
<td></td>
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<td></td>
<td></td>
<td>Male = female</td>
<td></td>
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</tr>
<tr>
<td>Plexiform schwannoma (PS)</td>
<td>Benign neoplasm originating from peripheral nerve sheath</td>
<td>Rarely found in the GI tract</td>
<td>–</td>
<td>Resection (local excision)</td>
<td>(74,75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histologic features: tumors with cellular growth pattern</td>
<td></td>
<td></td>
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</table>

GEJ, gastroesophageal junction; EMR, endoscopic mucosal resection; GI, gastrointestinal.
receptor 2 (HER2) (85-87). There is an active phase 1 study being conducted at the University of Oxford evaluating the combination of an ATR inhibitor with chemoradiotherapy in esophageal cancers in patients 16 years of age or older (ClinicalTrials.gov. NCT03641547). Table 1 lists the treatment strategies that have been reported in prior case reports, however no common treatment strategies are established in children.

Although esophageal neoplasms in childhood are rare, they should be considered in the assessment of pediatric patients presenting with symptoms of progressive dysphagia and weight loss or with underlying risk factors.

**Conclusions**

EoE is the most common pediatric esophageal inflammatory condition, second to GERD. The EoE field is rapidly evolving as the incidence and prevalence continue to rise. Since EoE often starts in childhood and progresses to adulthood, new studies and clinical guidelines involve joint effort from pediatric and adult specialists. In contrast, BE and esophageal neoplasms rarely occur in childhood. The relationship between a chronic inflammatory condition like EoE to BE and/or esophageal neoplasms is uncharted. However, increased awareness of and diagnostic screening for EoE in the pediatric population, might have some indirect effect on detecting BE and incipient esophageal neoplasms. Thus, future observational studies will be essential to exploring the relationships between these diseases.

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**Footnote**

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