

Treatment of Eosinophilic Esophagitis in Children

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Opinion statement

Eosinophilic esophagitis (EE) is an important esophageal disorder with distinct clinicopathologic features, and the condition is associated with a high prevalence of food allergies and atopy. In the past decade, we have improved our ability to recognize the phenotype of EE, but our ability to treat EE effectively remains limited despite several reports of successful treatment using elemental or elimination diets, and systemic and topical corticosteroids. The limitations for developing effective treatment regimens are due to some still unresolved and ambiguous aspects of the pathogenesis of EE. Neither the predisposing factors for developing EE in a subset of patients with atopy, nor the variable responsiveness to control measures for allergens are fully understood. There also remain questions about the precise role of gastroesophageal reflux, and the natural history of the disorder, contingent on which is the optimal treatment of EE. In devising treatment for a patient with EE, all attempts should be made to identify and control food and other allergies. In patients who have no diagnosed allergies or who are unresponsive to allergy treatment, topical steroids are a safe and effective treatment option. Systemic steroids should be reserved for those patients who are refractory to topical steroids. Beyond the initial phase of induction treatment, it is crucial to develop effective and safe maintenance treatment regimens based on ongoing allergen control and mast cell inhibitors. There are limited but encouraging data to support further exploration of the role of leukotriene and interleukin-5 inhibitors as safe, effective, and steroid-sparing treatment options.

Introduction

DEFINITION

Eosinophilic esophagitis (EE) is being increasingly recognized as a clinicopathologic entity distinct from gastroesophageal reflux disease (GERD). It is characterized by the presence of a dense epithelial eosinophilic infiltrate, more than 15 eosinophils per high-power field (eos/hpf) in a macroscopically ringed or furrowed esophagus (Fig. 1), and commonly presents with vomiting, chest pain, dysphagia, and food impactions in predominantly young men with a background of atopy who have failed to respond to antireflux therapies [1••,2,3•,4].

EPIDEMIOLOGY

There are no epidemiologic studies to date that pertain to the precise incidence and prevalence of EE; however, a miniepidemic of EE has been noted by the pediatric gastroenterology community in recent years. The approximately 133 pediatric cases in the literature since the first published report by Picus in 1981 [5] have made a major contribution to characterization and management of EE [3•,5–7,8,9,10••,11]. Several reports of a similar esophageal disorder afflicting adults have also appeared and have been referred to as defiant esophagus, small-caliber esophagus, and corrugated

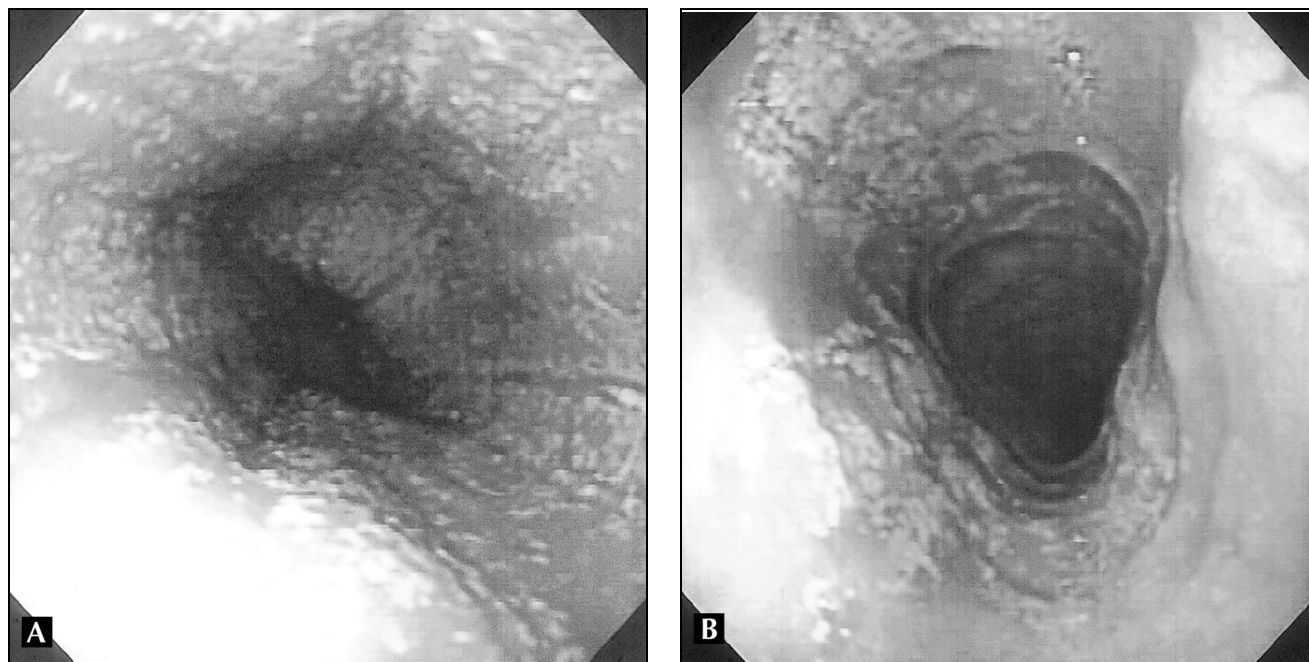


Figure 1. Endoscopy photographs showing the characteristic macroscopic appearance of furrowed (A), and ringed (B) esophageal mucosa with exudates in a patient with eosinophilic esophagitis.

ringed esophagus [12–15] in contrast with the more consistent pediatric usage of the term EE, probably representing the greater frequency of histologic sampling in grossly normal endoscopies in children. It is also speculated that a higher number of EE cases are diagnosed in children owing to the higher incidence of food allergies in the younger population.

PATHOGENESIS

Eosinophils have long been associated with allergies, but the link between allergens and EE has just begun to be elucidated. The hypothesis that food allergies produce EE is supported by observations assessing the symptomatic and histologic response to restricted and elemental diets in patients with EE. Moreover, some recent important observations have been made in animal models that support the role of aeroallergens in inducing eosinophilic inflammation in the esophagus by cytokine-mediated mechanisms shared with pulmonary inflammation [16••,17,18].

PRESENTATION

The clinical presentation of EE may be easily confused with GERD. Infants present with symptoms of vomiting, hematemesis, irritability, and failure to thrive, whereas older children and adolescents most commonly have obstructive esophageal presentations such as dysphagia, impactions, and strictures. Children of all ages with EE have been reported, although symptoms may peak in infancy and in 10- to 14-year-old individuals. The duration of symptoms before diagnosis may range from a few days to years depending on whether the

presentation is acute with food impaction or chronic with GERD-like symptoms [1••,2,3•,4,8••,9,19].

ASSOCIATIONS

There is a line of evidence for EE associated with food allergies, although these allergies are not always demonstrable by available laboratory tests. A fairly large number of patients with EE may have a personal (~ 60%) or family history (20% to 40%) of atopy, that is, allergic rhinitis, asthma, and dermatitis. Gastroesophageal reflux diagnosed by intraesophageal pH monitoring may be present in a smaller number of patients.

DIAGNOSTIC EVALUATION

The gold standard for diagnosis of EE is the presence of a dense eosinophilic infiltrate in the esophageal epithelium. According to most experts, an eosinophilic density of more than 15 eos/hpf in the esophageal squamous epithelium is strongly suggestive of EE and aids in differentiating it from GERD, which is usually associated with 5 eos/hpf or less [1••,3•,11]. The intermediate group of 5 to 15 eos/hpf remains an ambiguous entity and may represent allergies overlapping with GERD. Other notable pathologic findings in EE include superficial epithelial distribution of eosinophils, eosinophil aggregation, eosinophil abscess, and basal layer proliferation. In order to determine the cause of eosinophilic infiltration, further evaluation should be directed toward allergies (food and environmental), and other precipitants like parasitic infections, drug reactions, collagen vascular disease, and autoimmune disorders. Evaluation for food allergies rests on a complete history of foods suspected

Table 1. Overview of treatment outcomes for eosinophilic esophagitis in children

Treatment	Study	Number	Sex (men)	Age, y	Atopy, %	Family history of allergies, %	Skin/RASTs, %	Clinical outcome
Diet	Kelly <i>et al.</i> [8]	10	6	5	NA	NA	67	Resolved 8/ improved 2+
	Liacouras <i>et al.</i> [24]	127	86	10.45	50	45	NA	Improved 123
	Spergel <i>et al.</i> [20]	26	22	6.93	81	81	73	Resolved 18/ improved 6
Steroids	Faubion <i>et al.</i> [25]	4	4	12.5	25	25	NA	All resolved
	Liacouras <i>et al.</i> [10••]	20	NA	5.9	NA	NA	NA	Resolved 13/ improved 6+
	Teitelbaum <i>et al.</i> [26•]	13	NA	NA	NA	NA	69	Resolved 13

NA—not available; RASTs—radioallergosorbent tests.

of provoking symptoms; laboratory investigations include skin prick and in vitro tests by immunoglobulin (Ig) E-mediated radioallergosorbent tests (RASTs), but at present, non-IgE mediated reactions cannot be reliably diagnosed through any standardized test.

TREATMENT OVERVIEW

Much of the discussion in the following section is based on a limited number of published studies reporting experience with management of EE (Table 1). Elimination diets have been shown to be a successful initial therapeutic strategy in those patients with food allergies. In addition, identification of and subsequent control of associated atopy and environmental allergens is crucial to optimal therapy. Systemic and topical steroids have also been shown to be effective and recommended in patients with primary EE that is unassociated with food allergies and in those with poor compliance or response to elimination diets. Promising new treatment modalities based on antiallergy actions (*eg*, leukotriene

receptor antagonists and TH-2 cytokine inhibitors) have been explored to a limited extent in asthma, and they may be effective and safe alternatives to steroids in children with EE. Adjunctive treatment of gastrointestinal reflux is effective in ameliorating reflux-mediated symptoms. A few patients also benefit from periodic esophageal dilations for underlying strictures, along with dietary therapy and anti-inflammatory agents.

INDICATIONS FOR HOSPITALIZATION

There are no specific indications to hospitalize patients with EE, but infrequently, patients with the following complications may benefit from an in-patient evaluation aimed at diagnosis or treatment interventions:

- Failure to thrive
- Dysphagia with or without strictures accompanied by failure to ingest adequate nutrition
- Acute food impactions necessitating endoscopic intervention

Treatment

- There are no established guidelines specifically for the treatment of EE. The following discussion and algorithm (Fig. 2) are largely based on a review of the pediatric studies evaluating the response to dietary therapy, pharmacotherapy, and the role of endoscopic interventions in management of EE.

Diet and lifestyle

- Dietary modification has assumed great importance in the treatment of EE. The rationale for dietary therapy is based on eliminating antigenic exposure that is suspected to provoke allergic reactions. Many patients are unaware of a relationship of ingested foods with any symptoms, but all efforts should be made to identify food allergens by a obtaining a good history of food

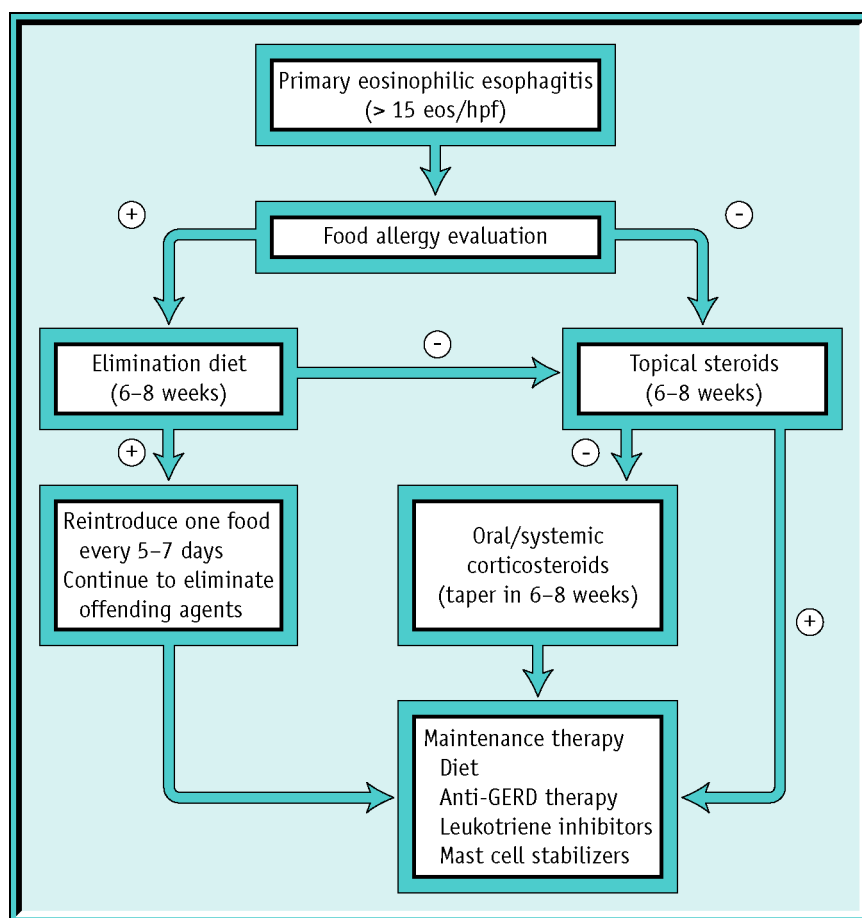


Figure 2. Algorithm for treatment of eosinophilic esophagitis. eos/hpf—eosinophils per high-power field; GERD—gastroesophageal reflux disease.

ingestion related to symptoms, skin prick, and RASTs. Patch skin tests have also been shown to be helpful in identifying non-IgE-mediated reactions in patients with EE [20]. It should be borne in mind that a small number of foods account for the majority of allergies: milk (2%), egg (1.3%), peanuts (0.5%), soy, wheat, tree nuts, and fish and shellfish comprising this group [21•,22•].

- Two prospective studies evaluating the efficacy of dietary restriction and elemental diet in children with EE for at least 6 weeks reported significant symptomatic and histologic improvement [8,20]. The results are particularly impressive in the context of negative allergy evaluation in some of these patients. Other reports also indicate a favorable role for dietary therapy in EE [3•,19,23,24]. Because it may take 2 to 6 weeks for symptoms to improve, dietary therapy should be maintained until a symptom-free state is attained, and then open food challenges may be conducted every 5 to 7 days. Open food challenges with close monitoring of clinical symptoms help in identifying offending foods and are the basis for long-term dietary treatment and facilitate discontinuation of antireflux treatment.
- The extent of dietary treatment depends on the results of food allergy evaluation, food challenge, age of the patient, and expected compliance. In using elimination diets, it is important to employ a nutritionist who could work with the family and emphasize the need for compulsiveness in reading nutrition labels, being familiar with different sources of the same protein (casein, caseinate, whey, and lactalbumin are all milk proteins), and being alert to possible contamination in the process of food preparation. Experts recommend three main types of elimination diet and a brief description of each follows [21•,22]:

- Elimination of one or more foods suspected of provoking symptoms, usually based on results of specific skin prick and in vitro reactions to food antigens. This diet is simple to institute for a limited number of established food allergies but impractical for chronic gastrointestinal symptoms and negative food allergy results.
- An oligoantigenic diet is recommended for chronic gastrointestinal complaints suspected to be on the basis of food allergies despite negative skin prick and in vitro results, and allows a certain number of foods in the diet that are considered unlikely allergens. The recommended diet has advantages of being nutritionally balanced and palatable while eliminating offending food proteins. Thus, foods typically allowed are vegetables (broccoli, lettuce, sweet potato, spinach, asparagus, and corn), cooked apple, rice, lamb, vinegar, olive oil, salt, and sugar.
- Elemental diet based on amino acid based formulas like Neocate, Neocate one plus, EO28 (SHS North America, Rockville, MD), Vivonex (Novartis, Minneapolis, MN) and EleCare (Ross, Columbus, OH) are recommended to patients when other restricted diets have failed and there is a strong suspicion that food allergies are producing symptoms. Elemental diets elicit poor compliance in older children owing to their extremely restricted nature and poor palatability, and they often have to be administered through a nasogastric tube. Elemental diets also impose a heavy financial burden on patients' families because many insurance carriers do not provide coverage. At present, there are no data comparing the cost effectiveness of dietary regimens with pharmacologic trials in patients with EE, but this factor should be an important consideration in the future owing to the often chronic and relapsing nature of this condition.
- The following recommendations on lifestyle are based on experimental models and clinical observations of pulmonary sensitization associated with EE:
 - Evaluation for atopy
 - Environmental control measures for known allergies
 - Pharmacologic therapy with antihistamines, bronchodilators, and mast cell stabilizers, as indicated

Pharmacologic therapy

- No pharmacologic therapy has been approved specifically for treatment of EE. However, there is accumulating evidence from the limited published experience that anti-inflammatory agents including steroids, by virtue of their broad anti-inflammatory actions, clearly benefit patients with EE; on the other hand, the role of mast cell stabilizers is less clear. By extrapolating the favorable experience with novel antiallergy medications in asthma and eosinophilic gastroenteritis to EE, it is hoped that future investigations will specifically evaluate their usefulness in EE. Overall, pharmacologic therapy for children with EE remains challenging because the natural history of the disease has not been well studied, none of the available medications has been approved by the US Food and Drug Administration (USFDA) but used outside the terms of their license, and the clear benefits of potentially effective treatments must outweigh the undesirable side effects for the pediatric population. Thus, the aims of drug therapy in children with EE are as follows:
 - Use of drugs proven to be overall safe and efficacious.
 - Use of drugs known to have specific actions against the cellular mediators of eosinophilic inflammation.

Corticosteroids

- Systemic and topical corticosteroids are clearly effective in short- and long-term treatment of EE in children who are unresponsive to antireflux and dietary therapy. Mechanisms of action include inhibition of eosinophil growth factors, interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor. The main indications for using steroids in EE are as follows:
 - Primary EE not associated with food allergies.
 - EE nonresponsive to elimination diets.

Systemic corticosteroids (methylprednisolone, prednisone)

	Systemic corticosteroids are potent anti-inflammatory drugs that have been approved for use in several inflammatory conditions. In steroid-treated EE, symptoms improve in 1 to 2 weeks and histologic improvement has been documented after 4 weeks of therapy, thereby strongly supporting their role in induction treatment [3•,9,10•,11]. Relapses may occur within 6 weeks after withdrawal of steroids but respond quickly to a repeat course of steroids.
Standard dosage	The doses used in EE, although not FDA approved for children, are similar to those used in most other gastrointestinal inflammatory diseases. The recommended initial treatment regimen using systemic steroids is a dose of 1 to 2 mg/kg body weight per day orally for 8 weeks, and then tapered doses should be given after 6 to 8 weeks.
Contraindications	Systemic fungal infections, varicella, herpes keratitis, and hypersensitivity to prednisolone.
Main drug interactions	Barbiturates, phenytoin, rifampin, vaccines, and toxoids.
Main side effects	Fluid and electrolyte disturbances (salt and water retention, hypertension), musculoskeletal (myopathy, osteoporosis, pathologic fractures), gastrointestinal (peptic ulcer disease, pancreatitis), dermatologic (impaired wound healing, ecchymoses, petechiae, increased sweating), neurologic (headaches, vertigo, pseudotumor cerebri), endocrine (Cushingoid state, growth suppression, secondary adrenocortical and pituitary unresponsiveness, glucose intolerance), ophthalmic (posterior subcapsular cataracts, glaucoma), and metabolic (negative nitrogen balance).
Special points	Steroids may cause gastrointestinal upset and should be taken with food.
Cost/cost effectiveness	There are no data pertaining to the cost effectiveness of this therapy in EE.

Topical steroids (fluticasone propionate and beclomethasone)

	The novel method of topical delivery of steroids to the esophagus was first reported by Faubion <i>et al.</i> [25]. Recently, Teitelbaum <i>et al.</i> [26•] have reported success using topical steroids in 13 children who either failed to respond to dietary therapy or had a negative allergy evaluation. Clinical and histologic response has been demonstrated within 1 week and 6 weeks, respectively, post-treatment and may last for 18 months. As much as 80% of inhaled corticosteroid in asthma patients is deposited in the esophagus. The topical delivery of steroids has been associated with fewer systemic side effects owing to reduced systemic absorption and the greater hepatic first-pass effect.
Standard dosage	Children 2 to 4 years of age, 44 µg/actuation; 5 to 10 years of age, 110 µg/actuation; 11 years of age and older, 220 µg/actuation, two puffs twice daily swallowed without inhaling and without use of a spacer. In one report, beclomethasone 42 µg/puff was administered effectively as four puffs twice a day through a metered-dose device without a spacer.
Contraindications	Hypersensitivity to any component.
Main drug interactions	None reported.
Main side effects	Oral and esophageal candidiasis are the major side effects reported with topical steroids, although hypopituitary-adrenal axis suppression, Cushing's syndrome, growth retardation, secondary infection, headache, dizziness, pharyngitis, nasal congestion, epistaxis, and dysphonia may be rare occurrences.

- Special points** The instructions for proper use are to swallow the medication and to rinse out the mouth after administration.
- Cost effectiveness** A 6-week treatment course using topical steroids is threefold more expensive than prednisone. However, the favorable safety and efficacy profile of topical steroids is more important than any cost consideration.

Mast cell stabilizers

- Cromolyn sodium is a mast cell stabilizer that inhibits T-cell functions and the release of leukotrienes and inflammatory cytokines. It is difficult to evaluate the role of this treatment in EE as most reports [3•,11] pertaining to its use also combined dietary therapy, steroids, and antireflux medications, but in eosinophilic gastroenteritis, a closely related disorder, cromolyn sodium has been an effective maintenance treatment [27].
- Standard dosage** Children 2 to 12 years of age should receive one ampule (100 mg/5 mL) four times a day 30 minutes before meals and at bedtime; children older than 12 years of age, two ampules four times a day before meals. Cromolyn sodium should be used with caution in children younger than 2 years of age at a maximum dose of 30 mg/kg/d in four divided doses.
- Contraindications** Known hypersensitivity to cromolyn sodium.
- Main drug interactions** In mice, an increase in major malformations was observed with coadministration of cromolyn sodium and isoproterenol.
- Main side effects** Most side effects are reported to involve the gastrointestinal system and are transient, and they include diarrhea, nausea, abdominal pain, constipation. Some less common side effects reported are skin rashes, myalgias, arthralgias, headaches, anxiety, depression, palpitations, abnormal hepatic functions, and pancytopenia.
- Special points** The effects of the medicine depend on its regular use. The liquid contents of an ampule should be emptied into a glass of water, stirred, and then fully ingested.
- Cost/cost effectiveness** There are no available data on the cost effectiveness of this therapy in EE.

Anti-GERD therapy

The role of GERD in the pathogenesis of EE is not well defined, but most published and anecdotal experience supports adjunctive antireflux therapy for synergistic effects. [3•,8,11,19] Secondary motility disturbances in the esophagus may predispose to GERD, and once the primary target (*ie*, allergens) is identified and treated, the antireflux medications can be discontinued. However, it may be prudent to assess the contribution of acid reflux by intraesophageal pH probes before instituting specific therapy. The efficacy of acid-suppressive regimens in improving symptoms and histology in EE should be evaluated in well-designed prospective trials. Readers are referred to recent published reviews on GERD therapy for specific details [28].

Interventional procedures

Esophageal food disimpaction

- Standard procedure** Flexible upper endoscopy, preferably under general anesthesia, for children is indicated for esophageal food disimpactions.

The American Society for Gastrointestinal Endoscopy recommends food bolus extraction with an overtube using a polypectomy snare, basket, or tripod to minimize trauma to the esophageal mucosa and to prevent aspiration. It is mainly indicated for a bolus too big to be pushed into the stomach or if the esophagus distal to the bolus cannot be negotiated [29,30].

However, the push technique of gently pushing the food bolus into the stomach with the tip of the endoscope has a reported success rate of 79% to 97%. It may be used if the endoscope can be safely passed by the bolus or if a bigger bolus can be fragmented and subsequently pushed in to the stomach [29,30].

Contraindications	Acute or incompletely healed esophageal perforation. Relative contraindications include bleeding disorders, pulmonary disease, recent esophageal surgery, pharyngeal and cervical deformity, and recent laparotomy.
Complications	Perforation and bleeding account for 0.3% of complications per procedure; other risks include aspiration, chest pain, fever, and bacteremia.
Special points	Antibiotic prophylaxis should be used for patients at risk for bacterial endocarditis, according to the recommendations of the American Heart Association.
Cost/cost effectiveness	The information related to cost effectiveness of these methods has not been evaluated.

Dilation

Standard procedure	All patients who are considered candidates for esophageal dilation must have a prior esophagogram to aid in selection of the most appropriate method. The procedure is performed in a patient who has had a standard fast, and it is performed with the patient usually under general anesthesia or conscious sedation. Mercury-weighted rubber bougies (Hurst blunt tipped, Maloney tapered tipped) may be used without endoscopic or fluoroscopic guidance, exert both axial and radial shearing forces, and are indicated for relief of dysphagia in patients with normal esophagograms but defiant esophagus, and for dilation of benign peptic strictures [15,31]. Wire-guided, tapered polyvinyl bougies (Savary) are used under endoscopic or fluoroscopic guidance; exert axial and radial shearing effects; are indicated for long, tight, tortuous strictures; and those associated with hiatal hernia, esophageal diverticula, and tracheoesophageal fistula repair [31]. Balloon dilators either passed over a guidewire or placed through the scope (TTS) are indicated for short strictures. They exert only radial forces and, in theory, reduce the risk of perforation [31].
Contraindications	The contraindications of dilation are same as those for endoscopic disimpactions.
Complications	The overall complication rate is 0.5% of all dilation procedures performed and, specifically, are the same as those for endoscopic disimpaction.
Special points	No more than three dilators of increasing diameter should be passed in a single session after first encountering moderate resistance. Strictures associated with EE are usually located in proximal to midesophagus in contrast to peptic strictures located in the distal esophagus.
Cost effectiveness	There are no studies that demonstrate the cost effectiveness or superiority of one method of dilation over another, although bougies may have the best safety record.

Other treatments

- Anti-IgE therapy using injections of humanized anti-IgE monoclonal antibodies for IgE-mediated sensitivities and modification of responsible antigens to produce safe varieties of foods otherwise regarded as allergenic are being investigated [22•].

Emerging therapies

- Based on data obtained from recently published animal studies elucidating the pathogenesis of EE, selective inhibitors of leukotriene (montelukast) and IL-5 (suplatast tosilate) could be promising new therapies for EE.

Montelukast

Indicated mainly for maintenance treatment of asthma, there are reports of montelukast use in eosinophilic gastroenteritis as an effective, safe, and steroid-sparing therapy [32–33].

Standard dosage	In asthma, the recommended dose is 4 mg/d for a 2- to 5-year-old child, 5 mg/d for a 6- to 14-year-old patient, and 10 mg/d for a patient older than 14 years of age.
Contraindications	Hypersensitivity to any component of montelukast.
Main drug interactions	Phenobarbital reduces the area under the curve ~40% after a single 10-mg dosage.
Main side effects	Headache, dizziness, rash, diarrhea, abdominal pain, elevated liver enzymes, hepatic eosinophilic infiltration, and cough.
Special points	Appropriate clinical monitoring is indicated when coadministered with potent P450 enzyme (CYP3A4 and 2C9) inducers.

Suplatast tosilate

Suplatast tosilate is a novel antiallergy drug that suppresses cytokine production, including IL-4 and IL-5 from TH-2 cells. In a double-blind randomized study in asthma, this drug has demonstrated a considerable steroid-sparing effect. There are no reports of its use in EE, but the single report of suplatast as an effective and safe treatment of eosinophilic gastroenteritis (300 mg daily) is encouraging [34].

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