



**EDUCATIONAL OBJECTIVE:** Readers will distinguish eosinophilic esophagitis from reflux disease based on specific clinical symptoms and histologic features

**DAVID A. KATZKA, MD**

Staff, Gastroenterology and Hepatology,  
Mayo Clinic, Rochester, MN

**TAKE-HOME  
POINTS FROM  
LECTURES BY  
CLEVELAND  
CLINIC  
AND VISITING  
FACULTY**

# The ‘skinny’ on eosinophilic esophagitis

## ABSTRACT

Eosinophilic esophagitis—a disease that even most physicians know little about—is becoming increasingly common. Often starting in childhood with eating difficulties and symptoms of gastroesophageal reflux disease, it progresses with increasing inflammation, fibrosis, and strictures until the esophagus is visibly narrowed on radiography. Early recognition and treatment with an allergen-avoidance diet and steroids are critical to avoiding or postponing complications.

## KEY POINTS

Eosinophilic esophagitis is an allergy-mediated, systemic disease.

It is diagnosed by characteristic symptoms, esophageal biopsy (peak value  $\geq 15$  eosinophils per high-power field), and response to allergen avoidance or treatment with steroids.

Therapy with a proton pump inhibitor should be tried even for patients with a classic presentation.

Strict dietary avoidance of allergens has been shown to resolve the disease but is often impractical.

Dilation is indicated for a narrowed esophagus but must be done cautiously because of the risk of tearing.

How best to monitor the disease (eg, by annual endoscopy) is still uncertain.

**E**OSINOPHILIC ESOPHAGITIS is a new disease defined by specific criteria that include a constellation of symptoms. Consensus guidelines define it as a chronic antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.<sup>1</sup>

Ten years ago, a biopsy that revealed eosinophils in the esophagus was diagnostic, because normally eosinophils are not seen in the esophagus. The current definition has evolved to become more comprehensive and includes clinical, demographic, and radiographic criteria.

This article presents an overview of eosinophilic esophagitis—its pathogenesis, epidemiology, clinical presentation, diagnosis, and management.

## ■ ALLERGIC ORIGIN

Eosinophilic esophagitis is best regarded as a systemic rather than a single-organ disease, although current treatments are mostly directed specifically at esophageal inflammation. Evidence is clear that eosinophilic esophagitis is allergy-mediated.

The current “two-hit” etiologic model involves exposure first to aeroallergens that prime the esophagus, followed by food allergens that cause an eosinophilic response with antigen recognition and stimulation of immune cells from the bone marrow. Other allergic avenues may also be present, including those involved with atopy, asthma, eczema, and food allergies, which stimulate the Th2 pathway and lead to esophageal eosinophilia and inflammation.<sup>2</sup>

The two-hit model is supported experimentally: the disease can be induced in mice by injecting ovalbumin under the skin as a sensitizing agent, then exposing the airway to an aerosol of *Aspergillus fumigatus*, producing an allergic reaction involving classic Th2 allergy

Medical Grand Rounds articles are based on edited transcripts from Medicine Grand Rounds presentations at Cleveland Clinic. They are approved by the author but are not peer-reviewed.

doi:10.3949/ccjm.82gr.14008

pathways.<sup>3</sup> Further evidence is that many patients report that asthma or rhinitis developed years before esophageal disease began.

Patients with eosinophilic esophagitis and their family members have a high prevalence of allergies, and the disease frequently flares up during allergy season. Endoscopic biopsy specimens from patients often reveal increased T cells, mast cells, interleukin (IL)-5, and tumor necrosis factor alpha, all of which stimulate eosinophil and are essential to an allergic reaction. They also have high levels of CD3, CD4, and CD1A antigen-presenting lymphocytes, which are all associated with allergy.

Eosinophilic esophagitis responds to allergy medications, including corticosteroids and IL-5 or IL-13 mast-cell inhibitors. The strongest evidence for an allergic etiology is that withdrawing culpable food allergens leads to resolution of the disease. Peterson et al<sup>4</sup> gave 18 adults with eosinophilic esophagitis an elemental diet (ie, a pure amino acid, carbohydrate-based diet in which all suspected allergens have been removed), and in 2 to 4 weeks, the mean number of eosinophils seen histologically fell from 54 to 10 cells per high-power field. The response was nearly complete ( $\leq 10$  eosinophils per high-power field) in 72% of patients. When patients resumed a normal diet, the eosinophil content increased substantially within a few days.

### Role of leaky tight junctions

Normally, the junctions between epithelial cells are tight, but many conditions, including allergic and autoimmune diseases, are now believed to involve altered permeability of this tissue. Tight-junction proteins play an important role in regulating antigen delivery and are modulated by cytokines. Activation of cytokines causes the membrane to become more permeable, allowing antigens to get through, leading to an enhanced reaction. In eosinophilic esophagitis, it is postulated that food antigens that pass through the leaky membrane activate CD1-antigen-presenting cells, which then initiate an allergic reaction.<sup>5-9</sup>

### PREVALENCE IS INCREASING

Eosinophilic esophagitis was first described in 1993 with a report of 12 patients who had dysphagia, normal endoscopy, no acid reflux, and

intraepithelial eosinophilia.<sup>10</sup> The authors recognized that these patients had a distinct disease.

Since then, the disease has increased in prevalence. Kapel et al<sup>11</sup> reviewed more than 74,000 endoscopy slides from a national pathology database and found 363 cases, with increasing prevalence during the study period from 2002 to 2005. Looking back further in a similar study, Whitney-Miller et al<sup>12</sup> found a 0.3% prevalence from the years 1992 to 2000 vs 3.8% from 2001 to 2004.

Sealock et al<sup>13</sup> reviewed the literature to assess the prevalence of eosinophilic esophagitis and found considerable variation depending on the populations sampled. One study from Sweden<sup>14</sup> found a prevalence of 0.4% by performing endoscopy in 1,000 randomly selected people from nearly 3,000 responders to a questionnaire on abdominal symptoms. A study based on a Swiss database<sup>15</sup> found only a 0.02% prevalence. Other studies show higher rates: a study from Florida that examined biopsy specimens from patients who underwent endoscopy for any reason found a prevalence of 1%.<sup>16</sup> Another US study found a 15% prevalence in patients with dysphagia.<sup>17</sup> Since these studies were done nearly a decade ago, we can expect the prevalence to be higher today.

Celiac disease has also been increasing in recent decades, as has gluten sensitivity. Allergies in general are on the rise worldwide, including asthma and atopic dermatitis. Theories as to the cause of these increases have focused on ambient antigens, food additives, proton pump inhibitors (PPIs), and the microbiome.<sup>18,19</sup>

### DIAGNOSING EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis is diagnosed with a combination of symptomatic, histologic, and radiographic findings (TABLE 1). The classic patient is a white male—a child, teenager, or young adult—with dysphagia.

A case series of 23 adult patients<sup>20</sup> found a mean age of 35 (age range 18 to 57), with a male preponderance (14:9). There is commonly a history of other allergies, including asthma, allergic rhinitis, and atopic dermatitis. Patients more commonly present with dysphagia than heartburn or other esophageal symptoms.<sup>11</sup>

**Eosinophilic esophagitis is a new disease defined by specific criteria**

### Endoscopic findings—eosinophils, later fibrosis

Finding eosinophils in the esophagus is non-specific and is not sufficient to make the diagnosis. Other systemic diseases can involve esophageal eosinophilia, including Churg-Strauss syndrome, Crohn disease, and helminthic diseases. Whether some are related to eosinophilic esophagitis or are independent is not well understood.

Characteristic findings on endoscopy include a corrugated or ringed appearance and linear furrows, resulting from fibrosis and scarring. “Micro-tears” may also be visible projecting linearly up the esophagus. Multiple white specks are signs of conglomerations of eosinophils and are easily confused with yeast infection. Strictures from scar tissue cause the mucosa to be tight and fragile, making the esophagus very susceptible to tearing during endoscopy.

After years of untreated disease, the esophagus becomes increasingly inflamed and fibrotic. Adult patients with eosinophilic esophagitis who were followed for a decade were found to develop increasing collagen deposition in which the submucosa or even the entire esophageal wall was diffusely fibrotic.<sup>21</sup>

### Radiographic findings—a narrow esophagus

On radiography, the esophagus may appear narrow—not uncommonly one-third to one-quarter the caliber of a normal esophagus. As the esophagus progressively narrows, both eating and treatment become extremely difficult.

### Symptoms are different in children and adults

Symptoms reflect the endoscopic changes over time. In children, the condition manifests with feeding difficulties, vomiting, symptoms of gastroesophageal reflux, and abdominal pain as signs of inflammation. As the esophagus becomes fibrotic, teenagers and young adults tend to present with strictures, dysphagia, and food impaction. Of patients who present to an emergency department with food impaction, the major cause is now eosinophilic esophagitis.<sup>22</sup>

It is important to pay attention to symptoms in children to diagnose the condition and start treatment early to prevent or postpone disease advancement. Medical therapy does not clearly reverse the fibrosis.

TABLE 1

### Diagnosis of eosinophilic esophagitis

Symptoms related to esophageal dysfunction, eg, eating difficulties, vomiting, gastroesophageal reflux, abdominal pain, dysphagia

Esophageal biopsy findings showing eosinophil-predominant inflammation (peak value  $\geq 15$  eosinophils per high-power field)

Mucosal eosinophilia isolated to the esophagus

Other causes of esophageal eosinophilia excluded

No response to a course of proton pump inhibitors (although some patients with eosinophilic esophagitis do respond)

Treatment response—dietary elimination or topical corticosteroids (strongly supports diagnosis but not required)

As in many chronic benign diseases, patients learn to compensate, so a careful history is essential. Many deny having a swallowing problem, but questioning may reveal that they have always been slow, picky eaters, consuming mostly soft foods and drinking fluids with every bite.

### Distinguishing eosinophilic esophagitis from gastroesophageal reflux disease

Distinguishing eosinophilic esophagitis from gastroesophageal reflux disease can be a challenge, as signs and symptoms overlap.

Veerappan et al<sup>23</sup> looked for predictors of eosinophilic esophagitis in 400 adults who underwent routine upper endoscopy, 6.5% of whom had eosinophilic esophagitis. They found significant overlap in medical history for patients with and without the disease; while a higher proportion of patients with eosinophilic esophagitis had a history of asthma, dysphagia, food impactions, dermatitis, and food allergies, these conditions also occurred in other patients.

Similarly, the classic endoscopic findings of eosinophilic esophagitis—rings, furrows, strictures, and plaques—also occur in other conditions.<sup>23</sup> Reflux disease can cause scarring from excess acid and may even be associated with eosinophils in the esophagus, indicative of a combination of allergy and reflux. A small-caliber esophagus is also occasionally present in patients with reflux disease.

Ambulatory pH monitoring has been recommended to help determine if gastroesoph-

**Eosinophilic esophagitis is a systemic disease rather than a single-organ problem**

**TABLE 2**

**Therapies for eosinophilic esophagitis**

Medications
Proton pump inhibitors
Corticosteroids
Montelukast
Avoidance of allergens
Mechanical (dilation of strictures)

ageal reflux is the cause of esophageal eosinophilia and to guide therapy. However, in a prospective study of 51 patients,<sup>24</sup> neither positive nor negative results of initial pH monitoring accurately predicted response to PPIs or steroid therapy. Another study found that half of patients with an eosinophilic esophagitis profile without evidence of acid reflux by pH monitoring responded to treatment with a PPI.<sup>25</sup>

This raises the question of whether some patients with eosinophilic esophagitis have more acid reflux than is detected by pH monitoring, or alternatively, whether PPIs have other, less-recognized effects besides reducing acidity. Investigators are now ascribing a host of anti-inflammatory actions to PPIs, including effects on antioxidants, inflammatory cells, endothelial cells, and the gut microflora.<sup>26</sup> And PPIs may alleviate eosinophilic esophagitis through anti-inflammatory effects rather than by inhibiting secretion of gastric acid.

**■ THREE TYPES OF THERAPY**

In general, three types of therapy are available for patients with eosinophilic esophagitis: medications, allergen avoidance, and esophageal dilation (TABLE 2).

**Medications:**

**Try a PPI first, then a corticosteroid**

A PPI should be tried even for patients with a classic presentation of eosinophilic esophagitis because some will respond, and long-term PPI therapy is preferable to long-term steroid treatment. Patients should be put on a 2-month

course and should then undergo repeat biopsy.

For patients who do not respond to a PPI, a corticosteroid or montelukast can be tried. Topical therapy is showing promise as both a short- and long-term option to bring about remission.<sup>27</sup> For administration, a corticosteroid (budesonide or fluticasone) is mixed with a viscous solution, such as water with honey or chocolate syrup, making it thick so it better coats the esophagus. The therapy can be very effective: in up to 8 weeks some patients have a 90% resolution of esophageal eosinophilia. However, about 5% of patients develop a yeast infection, and adrenal suppression is a concern but appears to be uncommon.

**Avoidance of allergens**

Because eosinophilic esophagitis is an allergic disease, eliminating allergens should be an effective treatment. Unfortunately, from a practical standpoint, elimination is very difficult. The elemental diet formula is expensive and unpalatable, making it impractical for a prolonged period.

Gonsalves et al<sup>28</sup> put 50 adult patients with eosinophilic esophagitis on a diet eliminating the six most common foods believed to trigger the disease—wheat, milk, nuts, eggs, soy, and seafood—and found a marked reduction in eosinophils in the proximal and distal esophagus after 6 weeks. Additional triggers that have been identified include rice, corn, and legumes.<sup>29</sup>

Unfortunately, maintaining a diet without the most commonly identified allergens is not easy. Although some very motivated patients can do it, it is especially hard for teens and young adults. Variations of the diet, such as eliminating just two foods, make following a plan easier. Omitting milk alone would benefit an estimated 20% of patients with eosinophilic esophagitis.

Identifying food triggers is a challenge in itself as there is no good noninvasive method of identifying the allergens. The radioallergosorbent test measures immunoglobulin (Ig) E, and the skin-prick test measures acute hypersensitivity, but neither is very sensitive for the Th2-mediated reaction involved in eosinophilic esophagitis. In early trials, endoscopy and biopsy were painstakingly performed with the removal and reintroduction of every sus-

**Long-term PPI therapy is preferable to long-term steroid therapy**

pected food allergen, requiring multiple biopsies weekly, which is impractical for safety and economic reasons.

Attempts are being made to devise less invasive methods of sampling the esophageal mucosa. Transnasal endoscopy—done as an outpatient procedure with topical anesthesia—is a possibility. Another possibility is the esophageal string test,<sup>30</sup> which involves swallowing a weighted capsule on a string and then, after an hour, pulling it up again and testing the tissue on the string.

The “cytosponge,” a new device currently under investigation, also uses a string delivery system. The patient swallows a sponge contained in a gelatin capsule and attached to a string. When the capsule dissolves in the stomach—a process that takes only a few minutes—the sponge expands. The string is then pulled up, causing the sponge to sample the esophageal mucosa and thus obtaining a histologic specimen. This method shows promise as an inexpensive and noninvasive way to monitor the disease, although larger studies are needed to establish efficacy.<sup>31</sup>

### Dilation—proceed with caution

Dilation can be an important therapy, especially in teenagers and adults with a fibrotic, narrowed esophagus.

Early on, the procedure often resulted in complications such as deep mucosal tears and perforations. Jung et al<sup>32</sup> retrospectively analyzed 293 dilations in 161 patients with eosinophilic esophagitis and found a deep mucosal tear in 27 patients (9%), three perforations, and one incidence of major bleeding. All complications resolved without surgery. Factors associated with increased risk of complications were luminal narrowing in the upper and middle third of the esophagus, a luminal stricture that could not be traversed with a standard upper endoscope, and use of a Savary dilator.

It is critical that dilation be done slowly—a

few millimeters at a time. Several sessions may be needed.

### TREATMENT DURING REMISSION IS CONTROVERSIAL

Unless the patient with eosinophilic esophagitis can consistently control the disease by avoiding allergens, the question arises of whether to continue treating a patient who is in remission.

On the one hand, there is no known risk of Barrett esophagus or malignancy when the condition is not treated, and weight loss is uncommon because patients tend to accommodate to the condition. However, the long-term consequences are uncertain. Allergies are chronic, and disease progression with more fibrosis should be prevented. Also, food impaction commonly occurs and this requires aggressive dilation, which is risky.

On the other hand, chronic steroid therapy involves risk. The optimum steroid dosage during remission and whether alternate-day dosing is adequate have yet to be determined.

Long-term trials are needed to answer these questions. In the meantime, most physicians tend to aggressively treat this disease, if not with specific food avoidance, then with steroid maintenance therapy.

### MONITORING THE DISEASE

Monitoring eosinophilic esophagitis by clinical indicators is difficult. Once fibrosis develops, symptoms often do not reflect underlying pathology. It may turn out that, as in Crohn disease, monitoring mucosal healing rather than symptoms may be best.

Until we know more about this condition, careful monitoring of patients is important. However, it is too early to give specific guidance, such as endoscopy every 2 months or annually. Whether the eosinophil count should be the critical consideration is also unknown. ■

**Eliminating milk alone would benefit 20% of patients**

### REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011; 128:3–20.
2. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009; 137:1238–1249.
3. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001; 107:83–90.
4. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013; 108:759–766.
5. Steed E, Balda MS, Matter K. Dynamics and functions of tight junctions. *Trends Cell Biol* 2010; 20:142–149.
6. Chang F, Anderson S. Clinical and pathological features of eosinophilic oesophagitis: a review. *Pathology* 2008; 40:3–8.
7. Orlando LA, Orlando RC. Dilated intercellular spaces as a marker of GERD. *Curr Gastroenterol Rep* 2009; 11:190–194.

8. **Blanchard C, Wang N, Stringer KF, et al.** Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; 116:536–547.
9. **Rothenberg ME, Spergel JM, Sherrill JD, et al.** Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010; 42:289–291.
10. **Attwood SE, Smyrk TC, Demeester TR, Jones JB.** Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993; 38:109–116.
11. **Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA.** Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008; 134:1316–1321.
12. **Whitney-Miller CL, Katzka D, Furth EE.** Eosinophilic esophagitis: a retrospective review of esophageal biopsy specimens from 1992 to 2004 at an adult academic medical center. *Am J Clin Pathol* 2009; 131:788–792.
13. **Sealock RJ, Rendon G, El-Serag HB.** Systematic review: the epidemiology of eosinophilic oesophagitis in adults. *Aliment Pharmacol Ther* 2010; 32:712–719.
14. **Ronkainen J, Talley NJ, Aro P, et al.** Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2007; 56:615–620.
15. **Straumann A, Simon HU.** Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; 115:418–419.
16. **Almansa C, Krishna M, Buchner AM, et al.** Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol* 2009; 104:828–833.
17. **Prasad GA, Talley NJ, Romero Y, et al.** Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. *Am J Gastroenterol* 2007; 102:2627–2632.
18. **Dellon ES, Peery AF, Shaheen NJ, et al.** Inverse association of esophageal eosinophilia with *Helicobacter pylori* based on analysis of a US pathology database. *Gastroenterology* 2011; 141:1586–1592.
19. **Björkstén B, Naaber P, Sepp E, Mikelsaar M.** The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999; 29:342–346.
20. **Roy-Ghanta S, Larosa DF, Katzka DA.** Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2008; 6:531–535.
21. **Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU.** Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003; 125:1660–1669.
22. **Desai TK, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT.** Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc* 2005; 61:795–801.
23. **Veerappan GR, Perry JL, Duncan TJ, et al.** Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. *Clin Gastroenterol Hepatol* 2009; 7:420–426.
24. **Francis DL, Foxx-Orenstein A, Arora AS, et al.** Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2012; 35:300–307.
25. **Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al.** Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011; 9:110–117.
26. **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.
27. **Straumann A, Conus S, Degen L, et al.** Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010; 139:1526–1537.
28. **Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I.** Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012; 142:1451–1459.
29. **Lucendo AJ, Arias Á, González-Cervera J, et al.** Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013; 131:797–804.
30. **Fillon SA, Harris JK, Wagner BD, et al.** Novel device to sample the esophageal microbiome—the esophageal string test. *PLoS One* 2012; 7:e42938.
31. **Katzka DA, Geno DM, Ravi A, et al.** Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014. pii: S1542-3565(14)00933-1. doi: 10.1016/j.cgh.2014.06.026. [Epub ahead of print]
32. **Jung KW, Gundersen N, Kopacova J, et al.** Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis. *Gastrointest Endosc* 2011; 73:15–21.

.....  
**ADDRESS:** David A. Katzka, MD, Department of Gastroenterology and Hepatology, Mayo Clinic, 200 1st St. SW Mayo East 9, Rochester, MN 55905; e-mail: Katzka.David@mayo.edu