

## **Eosinophilic Esophagitis**

Daniel B. Wright  
University of Sussex

Kamala London  
University of Toledo

Eosinophilic esophagitis (EE) occurs when there is an abundance of eosinophils, a type of white blood cell, in the esophagus. This can create severe problems for digesting food. It often requires tube-feeding of an elemental formula and taking corticosteroids. In the past this disorder, and other eosinophilic gastrointestinal disorders (EGIDs), were thought to be relatively rare. However, recent epidemiological research shows that we are experiencing a mini-epidemic of EE with prevalence rates estimated at above 2 per 100,000 in adults and above 4 per 100,000 in children. The disorder is often misdiagnosed and therefore it is critical that more people are made aware of this disorder. This paper provides a review of the disorder and its treatment.

Eosinophils are a type of white blood cell thought to be important for defending against certain parasites and possibly involved in the development of certain organs.[1] Eosinophilic disorders are characterized by an abundance of eosinophils in the blood (eosinophilia) and different organs. When eosinophils accumulate in the gastrointestinal tract, these disorders are referred to as eosinophilic gastrointestinal disorders, or EGIDs.[2] The name of the specific disorder depends on where in gastrointestinal tract the abundance of eosinophils are, so eosinophilic colitis refers to the large intestine, eosinophilic enteritis refers to the small intestine, etc. The most common of these is eosinophilic esophagitis (EE), where large numbers eosinophils ( $> \sim 15\text{-}25$  in high power field [hpf] or  $.44\text{mm}^2$ ) are in the esophagus without any other explanation like leukaemia, parasitic infection, or reflux disease. We are experiencing a mini-epidemic of EE.[3,4] While EE can damage the esophagus and be extremely painful, many treatments can be effective even though they can be difficult to adhere to (e.g., tube feeding) and have their own negative effects (e.g., long term steroid use). It is important to raise the awareness of all eosinophilic disorders because they are often misdiagnosed.

Below we describe EE, review some data showing the increase in EE, discuss methods for diagnosis and treatment, and end with a plea for better recognition of this disorder and further research.

### ***Eosinophilic Esophagitis (EE)***

Eosinophils develop in bone marrow and are then released into the circulation.[1] Some target particular organs and others respond to allergens. They are composed of toxins which assist in their role in the immune system, but this also means their prolonged presence can be damaging. EE occurs when they reside in large numbers in the esophagus, where normally there are no eosinophils. Over the past several years, the cause of EE has become an active area of research, but as yet is unresolved.[2,5] Most people with EE have allergies and respond to changes in their diet, implicating an allergic aetiology. More research is necessary to understand the causal mechanisms implicated in EE and other eosinophilic disorders.

### ***Is EE Increasing?***

A recent cover story of *Today's Dietician* addressed EE, calling it a "rapidly emerging chronic illness in both paediatric and adult gastroenterology" (p. 29). The diagnosis of EE is rapidly increasing, and recent studies estimate its prevalence to be above 2 per 10,000 in adults and above 4 per 10,000 in children.[3,4] There are two reasons why statistical estimates of a disease's prevalence can increase. The first is that

more people become aware of it and the diagnosis improves. Because the symptoms of EE are often difficult to distinguish from gastroesophageal reflux disorder (GERD), many patients are first labelled with severe GERD before detailed analysis of a biopsy shows EE.[5] However, there is strong evidence that the increase in EE is not just due to better diagnosis, but that the disease is becoming more common. The largest study of prevalence in Europe [4] found over a 15 year period adult prevalence increased from 0.2 per 10,000 to 2.3 per 10,000. The demographics of the area they studied (Olten County in Switzerland) remained stable over this time, and they recorded the biopsies in a similar manner. Thus, the increase looks like an actual increase in the disease.

At present there are no comparable data from the UK. The number of people contacting UK based groups (TEDS - The Eosinophilic Disorder Society, and FABED - Families Affected By Eosinophilic Disorders) is increasing, but this does not provide good estimates of prevalence.

### ***Symptoms and Diagnosis***

EE is more common in males (estimates vary, but most are above 2 times higher than in females), and appears more common in children, though because research into EE is recent (most of the articles on EE have been published in the last 5 years) little is known about the progression of the disease. There is evidence for a familial association.[7] People with EE exhibit a wide variety of symptoms, which can make diagnosis difficult.[4,7,8] People with EE often show allergic reactions, failure to thrive, vomiting, and dysphagia (difficulty swallowing), and will often experience pain in the chest and digestive systems. Most have allergies to certain foods and non-foods, and therefore tests for these are an important first step. When an endoscopy is conducted there is often macroscopic abnormalities, but these are also common with GERD (and are not always present in EE). Because of the dysphagia and endoscopic findings, GERD is often explored as a possible cause, and treatment for acid suppression is used.[5]

Because endoscopies cannot provide conclusive diagnosis, microscopic analysis of biopsies of the esophagus is necessary to diagnose EE. Normally eosinophils are not present in the esophagus, but they can occur in relatively small numbers due to allergic reactions, recurrent vomiting, and a number of disorders. For example, in GERD, there may be some eosinophils, but usually less than 7 per hpf.[2] The number of eosinophils necessary for an EE diagnosis is not standardized, yet, but is approximately >24 in at least 2 hpf.[9] Therefore, the recommendation is that after allergens and other possible causes for heightened levels of eosinophils are eliminated, a biopsy is conducted. Not all people with EE show gross esophageal damage and eosinophils will not be uniformly distributed, consequently, microscopic inspection of tissues taken at multiple locations is necessary.

### ***Treatment***

Because people are only becoming aware of the prevalence of EE, the natural history of EE is unclear, but it seems that few people have a 100% recovery without treatment. Even if symptoms subside, eosinophils may still reside in the esophagus and cause long-term damage. No randomised controlled trials for different treatments have been completed but some are ongoing and recruiting.[10] There are two main types of treatment: diet and steroids. Because of the associations between EE and allergies, restricting diets is an obvious possibility and in most patients this reduces both the eosinophils and the symptoms.[11] There are difficulties with this approach. Identification of which foods to eliminate may be difficult because reaction to a particular food may take several days to occur and if the patient has consumed several foods over this time

precise identification may be impossible. Moreover, some people with EE react to an extremely large number of foods so that treatment will require acquisition of nutrients from an elemental (non-protein amino-based) formula. However, because of the importance of eating at many social events, this treatment can be debilitating, particularly for children (consider not having cake at your own birthday party). Further, it can be difficult to gain enough calories from elemental formula (digesting even liquid can be painful), and therefore tube-feeding is sometimes necessary.

The second treatment, systemic corticosteroids (usually fluticasone), a drug often used to control asthma, has been shown to reduce eosinophils and symptoms. For example, all 19 of Remedios and colleagues' [12] patients had fewer symptoms and most considerable fewer eosinophils post-treatment. However, after delay symptoms re-occurred in most of the patients, and 3 developed esophageal candidiasis.[13]

Both with and without treatment, symptom severity fluctuates. Even without clear symptoms, eosinophils may still be present and causing damage. Therefore, it is worth repeating biopsies, not just of the esophagus, but of the entire gastrointestinal tract. Current treatments can be effective, but are not without problems.

### **The Future**

EE was first reported in 1978.[14] It is now experiencing a mini-epidemic and this needs to be addressed. Because until recently there were few known cases, there was also little research. In recent years there has been an increase in research examining the causes of EE, the extent of the disorder, and possible treatments. If the prevalence rates in the UK are similar to those found in studies in Switzerland and USA, then many patients are being misdiagnosed. Discussions with UK families show misdiagnosis does occur. It is critical to improve awareness of EE, thus aiding accurate and prompt diagnosis, which will in turn fuel future research to improve understanding and treatment of EE.

1. Research shows that we are experiencing a mini-epidemic of eosinophilic esophagitis (EE).
2. EE is often misdiagnosed. Accurate diagnosis requires microscopic analysis of a biopsy.
3. Research into the causes of EE and treatments for EE is an active, though recent, area of medical research.
4. It is critical to raise awareness of EE.

1. Rothenberg, M. E., & Hogan, S. P. (2006). The eosinophil. *Annual Review of Immunology*, **24**, 147-174.
2. Rothenberg, M. E. (2004). Eosinophilic gastrointestinal disorders (EGID). *Journal of Allergy and Clinical Immunology*, **113**, 11-28.
3. Noel, R. J., Putnam, P. E., & Rothenberg, M. E. (2004). Eosinophilic esophagitis. *New England Journal of Medicine*, **351**, 940-941.
4. Straumann, A., & Simon, H-U. (2005). Eosinophilic esophagitis: Escalating epidemiology? *Journal Allergy and Clinical Immunology*, **115**, 418-419.
5. Noel, R. J., & Tipnis, N. A. (2006). Eosinophilic esophagitis: A mimic of GERD. *International Journal of Pediatric Otorhinolaryngology*, **70**, 1147-1153.

6. Yeager, V. (2006). Eosinophilic esophagitis: Climbing to new understandings. *Today's Dietician*, **8**, 28-32.
7. Guajardo, J. R., Plotnick, L. M., Fende, J. M., Collins, M. H., Putnam, P. E., & Rothenberg, M. E. (2002). Eosinophilic-associated gastrointestinal disorders: A world-wide-web based registry. *Journal of Pediatrics*, **141**, 576-581.
8. Parfitt, J. R., Gregor, J. C., Suskin, N. G., Jawa, H. A., & Driman, D. K. (2006). Eosinophilic esophagitis in adults: Distinguishing features from gastroesophageal reflux disease: A study of 41 patients. *Modern Pathology*, **19**, 90-96.
9. Personal communication with Alex Straumann, 13 June 2006. A group of experts are currently devising standards for diagnosis.
10. Kukuruzovic, R. H., Elliott, E. J., O'Loughlin, E. V., & Markowitz, J. E. (2006). Non-surgical interventions for eosinophilic oesophagitis (Cochrane Review). *The Cochrane Library*, **2**. <http://www.cochrane.org/reviews/en/ab004065.html>
11. Kelly, K. J., Lazenby, A. J., Rowe, P. C., Yardley, J. H., Perman, J. A., Sampson, H. A. (1995). Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. *Gastroenterology*, **109**, 1503-1512.
12. Remedios, M., Campbell, C., Jones, D. M., & Kerlin, P. (2006). Eosinophilic esophagitis in adults: Clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointestinal Endoscopy*, **63**, 3-12.
13. Kanda, N., Yasuba, H., Takahashi, T., Mizuhara, Y., Yamazaki, S., Imada, Y., Izumi, Y., Kobayashi, Y., Yamashita, K., Kita, H., Tamada, T., & Chiba, T. (2003). Prevalence of esophageal candidiasis among patients treated with inhaled fluticasone propionate. *American Journal of Gastroenterology*, **98**, 2146-2148.
14. Landres, R. T., Kuster, G. G. R., & Strum, W. B. (1978). Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology*, **74**, 1298-1301.

We wrote this in late 2006. Further information is available from [www.apfed.com](http://www.apfed.com).