



Primary eosinophilic disorders of the gastrointestinal tract

B M Yan and E A Shaffer

Gut 2009;58;721-732; originally published online 3 Dec 2008;
doi:10.1136/gut.2008.165894

Updated information and services can be found at:
<http://gut.bmj.com/cgi/content/full/58/5/721>

These include:

References

This article cites 109 articles, 19 of which can be accessed free at:
<http://gut.bmj.com/cgi/content/full/58/5/721#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections

Articles on similar topics can be found in the following collections

[GUT Recent advances in clinical practice](#) (24 articles)

Notes

To order reprints of this article go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to *Gut* go to:
<http://journals.bmj.com/subscriptions/>

Primary eosinophilic disorders of the gastrointestinal tract

B M Yan, E A Shaffer

Division of Gastroenterology,
Department of Medicine,
University of Calgary, Calgary,
Alberta, Canada

Correspondence to:
Professor E A Shaffer, University
of Calgary, Division of
Gastroenterology, Room 6D48,
Teaching Research & Wellness
Building, 3280 Hospital Drive
NW, Calgary, Alberta, Canada,
T2N 4N1; shaffer@ucalgary.ca

Revised 7 November 2008
Accepted 18 November 2008
Published Online First
3 December 2008

ABSTRACT

Eosinophils are important effector cells of the innate immune system. Eosinophilic infiltrative disorders of the gastrointestinal tract, though recognised for decades, have recently witnessed a resurgence of interest, particularly for oesophageal disease. A more comprehensive basis for eosinophilic infiltration and activation has identified interleukin 5 (IL5) as a key cytokine for the differentiation and proliferation of eosinophils, while eotaxins promote the recruitment of mature eosinophils to the gut. When activated, eosinophils release multiple cytotoxic agents and immunomodulatory cytokines, resulting in local inflammation and tissue damage. Although eosinophils normally convey a defence against unwanted interlopers such as parasites, in the absence of such inciting agents, their accumulation and activation can elicit the primary infiltrative disorders of the gut: eosinophilic oesophagitis, gastroenteritis and colitis. Diagnosis of these disorders is dependent on the clinical presentation, endoscopic findings (particularly for eosinophilic oesophagitis), and most importantly, histological confirmation. Dietary modifications and topical corticosteroids are first-line treatments for eosinophilic oesophagitis. Systemic corticosteroids are the mainstay of treatment for eosinophilic gastroenteritis; surgery may be required depending on the layer of mucosa involved. Eosinophilic colitis most often occurs in infants; removal of the causative allergen usually results in a complete response. Steroids may be required for older children/adolescents or adults. This review summarises current knowledge on the trafficking of eosinophils to the gastrointestinal tract and the clinical management of the primary disorders of eosinophilic oesophagitis, eosinophilic gastroenteritis and eosinophilic colitis.

The gastrointestinal tract is a constant battlefield between challenges from the external environment and the internal milieu of the body which seeks to maintain homeostasis. With a vast epithelial surface exposed to foreign (potentially toxic) substances, the alimentary tract employs defences, particularly its immune system. This must be exquisitely balanced to exclude toxic agents and organisms while simultaneously allowing the efficient absorption of nutrients essential to life. Eosinophils are key effector cells of the innate immune system within the gastrointestinal tract. These cells are customary inhabitants of the gastrointestinal tract, except for the oesophagus. In an evolutionary sense, intestinal eosinophils protect vertebrates against parasitic infestations, particularly helminths. Although the rate of parasitic infections in humans has decreased markedly in the developed world, there has been

a substantial rise in atopic/allergic disorders. As a result, hypersensitivity responses to allergens may be a driving factor towards recruitment and activation of gut eosinophils. There has been a resurgence of interest in eosinophilic gastrointestinal disorders over the last 20 years, particularly eosinophilic oesophagitis. Eosinophilic gastrointestinal disorders are a heterogeneous group of diseases, which are often grouped into primary (idiopathic) disorders and secondary eosinophilic disorders (inflammatory, infectious or hypersensitivity illnesses resulting in gut eosinophilia). This article reviews the physiology of gut eosinophils and the primary eosinophilic disorders: eosinophilic oesophagitis, eosinophilic gastroenteritis and eosinophilic colitis.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF EOSINOPHILS

Origin of the eosinophil

Eosinophils were first described over century ago as granular white blood cells that stained readily with eosin. These “acid-loving” granulocytes (“acidophils”) are the predominant inflammatory cell involved in allergic and parasitic disorders in vertebrates.

Eosinophils begin life and reside in the bone marrow for 8 days while undergoing maturation. Eosinophils subsequently relocate into the peripheral circulation for 8–12 h and finally traffic to specific tissues, predominantly the gastrointestinal tract, where they reside for at least 1 week.

Several inflammatory mediators and chemoattractants enhance eosinophil development, migration and effector function. Differentiation of haematopoietic stem cells to eosinophils in the bone marrow is dependent on a number of cytokines and growth factors. In the presence of interleukin 1 (IL1), IL3 and granulocyte macrophage colony stimulating factor (GM-CSF), primitive stem cells become eosinophilic precursor myeloblasts.¹ The terminal differentiation into eosinophils and any proliferation thereafter is critically dependent on the presence of IL5.^{2,3} Transgenic (Tg) mice that over-express IL5 under control of the T cell promoter CD2 (CD2 IL5 Tg mice) exhibit a 20-fold increase in eosinophils in haematopoietic organs.⁴ In contrast, mice that are deficient in IL5 (IL5^{-/-} BALB/c Tg mice) have decreased circulating eosinophils (by 80%) and decreased gastrointestinal eosinophils (50%) compared with control (wild-type) mice. Similarly, mice deficient in the functional receptor of IL5 (β -deficient mice, C57BL/6) have decreased peripheral

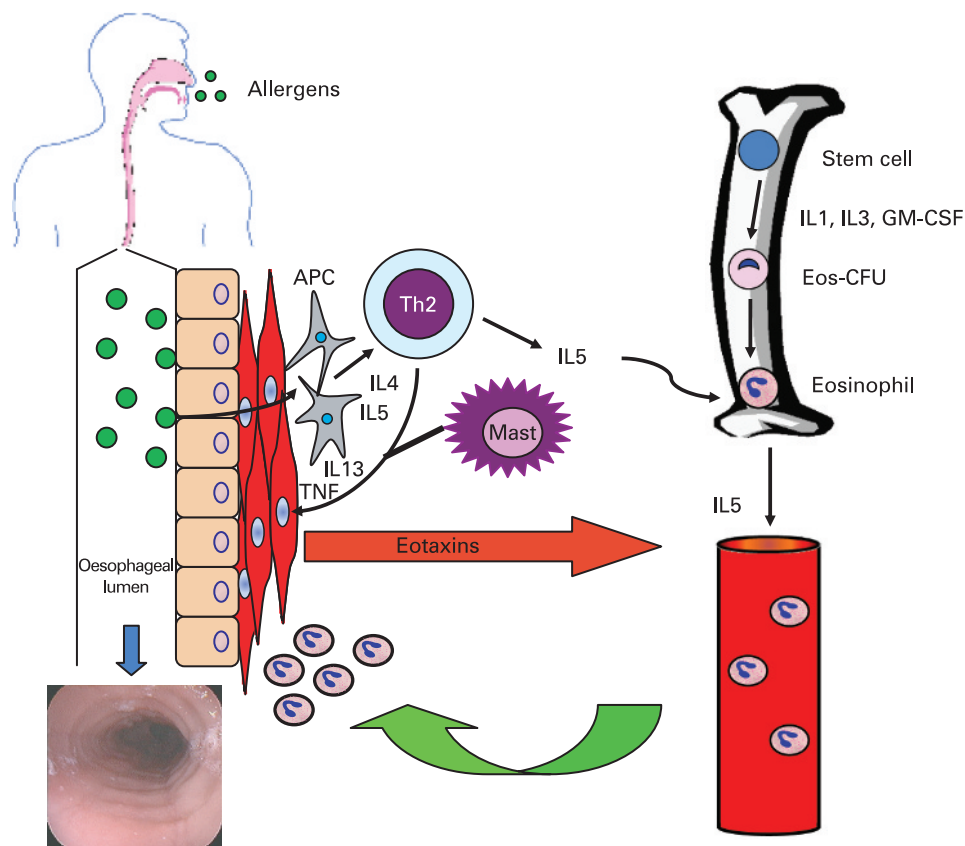


Figure 1 Homing of eosinophils to the oesophagus. Eosinophilic precursors (colony forming units) (Eos-CFU) are generated in the bone marrow under the influence of interleukin 1 (IL1), IL3, and granulocyte macrophage colony stimulating factor (GM-CSF). Patients are exposed to allergens (food or air). Antigen presenting cells (APCs) process these antigens and present them to helper T lymphocytes (Th2). Activated Th2 cells produce IL5, which is critical for the terminal differentiation and proliferation of eosinophils. IL4 is also produced by Th2 cells, which promotes eosinophilic accumulation and immunoglobulin E (IgE) production from B cells. In addition, Th2 cells and (activated) mast cells release IL13 and tumour necrosis factor (TNF) which promote local inflammation. Gastrointestinal epithelial cells produce eotaxins, which has essential chemokine activity for the recruitment of circulating eosinophils to the site of inflammation. As a result, mature eosinophils accumulate in the oesophagus, are activated, and degranulate releasing multiple cytotoxic agents. Chronic inflammation leads to architectural changes to the oesophagus as manifested in this diagram by mucosal rings, linear furrows, and adherent white exudates.

circulating and gastrointestinal eosinophils. Interestingly, as bone marrow eosinophils are only slightly reduced in either IL5 deficient or IL5 receptor deficient mice, other factors must be responsible for maintaining basal levels of eosinophils.⁵

Only a small number of mature eosinophils normally circulate in the peripheral blood. Rather, eosinophils are predominantly tissue-dwelling cells with greatest affinity for epithelial surfaces that interact with the external environment (eg, skin, lung and gastrointestinal tract). Eosinophils customarily reside in haematopoietic tissue and in the lamina propria of the gastrointestinal tract, the exception being the oesophagus.^{6,7} Within the lamina propria, eosinophils are ideally situated to protect against parasitic infestation. Resident eosinophils in the gastrointestinal tract do not evoke either an inflammatory reaction or cause tissue damage under normal circumstances.^{4,5} When provoked, eosinophils become activated to degranulate, releasing multiple cytotoxic agents to rid the body of the noxious agent or organism, but

they also can result in local tissue damage and dysfunction. Eosinophils are mediators of allergic responses such as atopic dermatitis, allergic rhinitis, asthma and eosinophilic disorders of the gastrointestinal tract.

Trafficking of eosinophils to the gastrointestinal tract

Homing of eosinophils to the oesophagus is shown in fig 1. Eosinophils initially home to the gut in the prenatal period, independent of bacterial flora.⁵ Although IL5 is important in regulating circulating levels of eosinophils, their accumulation in the gastrointestinal tract depends on a synergistic effect with eotaxin. Over-expression of IL5 in CD2 IL5 Tg mice results in a 4-fold increase in eosinophils in jejunal lamina propria and an almost 50-fold increase in oesophageal eosinophils, compared to wild-type mice.⁵ Conversely, mice deficient in eotaxin (CD2 IL5 Tg eotaxin $-/-$) have a significantly reduced number of jejunal eosinophils (by $\sim 90\%$), whereas peripheral eosinophils increase

2-fold.⁵ Therefore, the absence of eotaxin dramatically reduces eosinophils accumulating in the gut despite an elevated IL5 and the presence of increased circulating eosinophils. Thus, IL5 is important for upregulating eosinophilic differentiation by haematopoietic organs and controlling peripheral circulating eosinophil levels, whereas eotaxin is required for trafficking and accumulation in the gastrointestinal tract.

Eotaxin is a member of the chemokines (termed CC) family and was initially discovered in a rodent model for asthma and allergen-induced lung eosinophilia.⁸⁻⁹ Subsequently, human eotaxin was cloned and shown to be a specific chemoattractant for eosinophils.¹⁰⁻¹¹ Human genomic analyses have led to two further eosinophilic specific chemokines, named eotaxin 2 and 3.¹²⁻¹³ Eotaxin 2 and 3, however, are located on a different chromosome and only share 30% sequence homology to eotaxin 1.⁹ The receptor for all eotaxins is CCR3 which is highly expressed on eosinophils. Eotaxins play a major role in regulating eosinophil levels in the gut, as demonstrated by a constitutive high expression of eotaxin mRNA by intestinal cells.¹⁰⁻¹⁴ Eotaxin-1 deficient mice (eotaxin^{-/-} 129/SvEv mice) exhibit markedly reduced intestinal eosinophils in the absence of change in peripheral, splenic or marrow eosinophils.⁵⁻¹⁵ Similarly, CCR3 deficient mice have decreased baseline eosinophils (but increased splenic eosinophils) and do not recruit eosinophils when infected with *Trichinella spiralis*.¹⁶ Eotaxins therefore have a critical role for recruiting eosinophilic to the gastrointestinal tract.

Activation of eosinophils

Eosinophils respond to a number of stimuli including non-specific tissue injury, allergens and infections (fig 2). Recruitment and activation of eosinophils to sites of inflammation is regulated by cytokines, including IL5, IL13, IL4 and tumour

necrosis factor (TNF) produced by activated Th2 and mast cells.¹⁷⁻¹⁸ Activation results in degranulation, upregulated cytokine production, and IgE production. Pre-formed granules contain four major cationic proteins, all of which are cytotoxic: eosinophil peroxidase (EPO), eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and major basic protein (MBP). In addition, ECP and EDN have ribonuclease activity. MBP increases smooth muscle reactivity and can directly induce degranulation of mast cells and basophils. Eosinophils also generate large quantities of leukotriene (LT) C4, which is then metabolised to LTD4 and LTE4. All three are potent smooth muscle constrictors. Eosinophils produce a wide range of cytokines that potentiate the inflammatory response including IL1, IL3, IL4, IL5, IL6, IL8, GM-CSF, transforming growth factor (TGF) α/β , TNF, and eotaxin. Eosinophils therefore act not only as effector cells, but also as immunoregulatory cells.

EOSINOPHILS IN GASTROINTESTINAL DISEASE

Although first described in 1930s, eosinophilic gastrointestinal disorders did not receive great attention until the last decade. Publications have exponentially risen in the last decade, in particular for eosinophilic oesophagitis (fig 3). Eosinophilic disorders of the gastrointestinal tract can be separated into primary or secondary eosinophilic diseases: primary having no inciting cause, and secondary due to other illnesses resulting in eosinophilia.⁹ These gastrointestinal inflammatory disorders involve eosinophils but most patients also have a common feature of food-specific IgE and atopy, without food-induced anaphylaxis. Their features seem more related to cellular-mediated hypersensitivity from eosinophils rather than humoral (IgE) hypersensitivity.

Eosinophilic oesophagitis

Eosinophilic oesophagitis (EO), first reported in 1977, has gained widespread recognition over the past decade.¹⁹⁻²¹ Eosinophilic infiltration of the oesophagus can arise from acid-pepsin reflux into the reflux oesophagitis (GORD)²² but EO is a distinct entity, likely the product of a genetic basis, requiring allergens for expression.²³⁻²⁴ The differential diagnosis for eosinophilic oesophagitis and eosinophilic gastrointestinal disorders is shown in table 1.

Epidemiology and natural history

EO affects all ages and all ethnic groups, although reports have been selective, emanating predominantly from developed, industrialised countries. Population-based findings in children suggest an incidence of 1 in 10 000 and a prevalence of 4 in 10 000.²⁵ An Italian study estimated a rather high prevalence of 3.5% in children.²⁶ There appears to be a familial aspect to EO, implicating genetic factors.²⁷ In adults, large studies are lacking, but estimates suggest an incidence of 2–6 per 10⁵/year

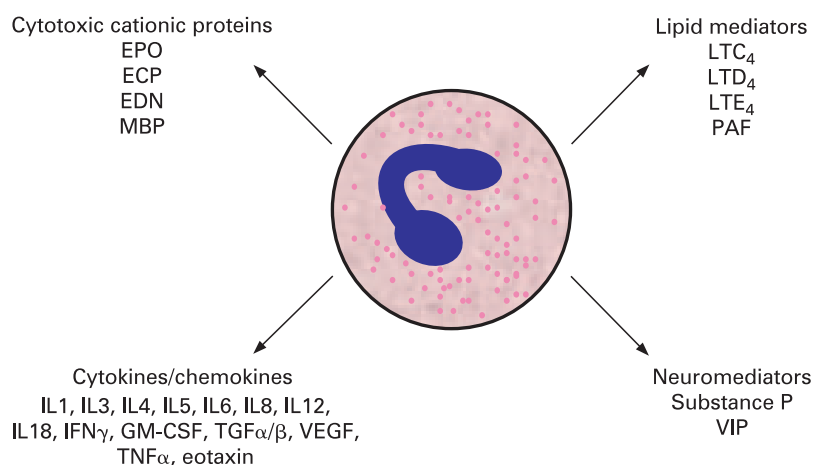


Figure 2 Mediators released by activated eosinophils. This figure is modified from Rothenberg.⁹ ECP, eosinophilic cationic protein; EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; GM-CSF, granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukin; LT, leukotriene; MBP, major basic protein; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide.

Recent advances in clinical practice

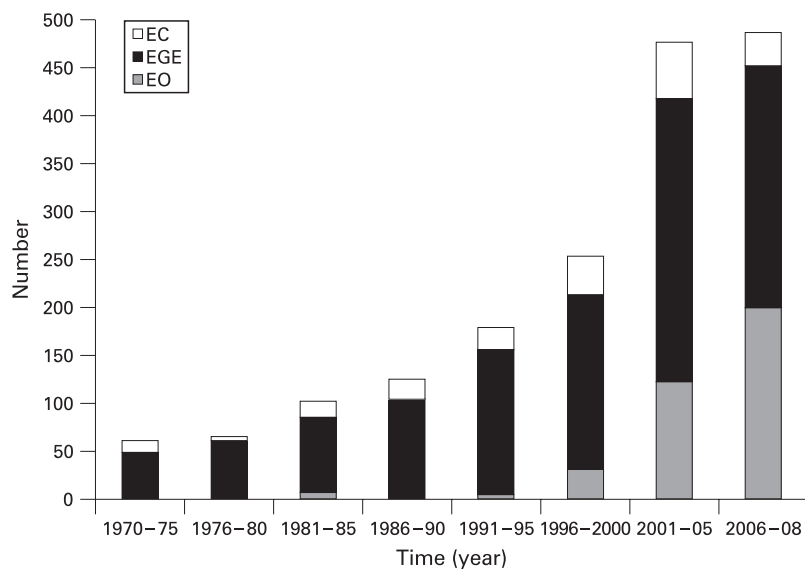


Figure 3 PubMed search for “eosinophilic oesophagitis” (EO), “eosinophilic gastroenteritis” (EGE) and “eosinophilic colitis” (EC). Relatively few publications were available prior to 1995. From 2000 to 2008 there has been a surge of publications related to eosinophilic disorders of the gastrointestinal tract. In particular for eosinophilic oesophagitis, publications have risen exponentially since 1991.

and a rising prevalence over a 16 year period from 2 per 10^5 to 27 per 10^5 .²⁸ Population-based data from an urban Canadian centre yield a combined children and adult incidence of 7.2 per 10^5 /year.²⁹ Prevalence from a large database in the United States indicates that EO occurs at any age (not just children); in adults it occurs most commonly in the 30s and 40s.³⁰ There is a male predominance at 3:1 male to female ratio. Food impaction has a high pre-test probability for the disease; some 50% of cases with food bolus impaction are related to it.^{31, 32} In a population study of upper endoscopies performed in 1000 (randomly selected) Swedish adults, 5% had increased eosinophils (many also had GORD), while 0.4% had definite eosinophilic oesophagitis.³³ Thus EO is more frequent in children and young male adults; its primary associations are with a personal and family history of other allergic conditions. Indeed, the incidence of the disease appears to be rising, in part due to increased recognition.^{28, 34}

Its natural history reveals fluctuating symptoms that appear to correlate with seasonal variability and exposure to exogenous allergens. A disproportionately increased frequency of EO is diagnosed in late summer/fall, supporting the putative role of inhaled allergens.³⁵ In long-term follow-up of adults³⁶⁻³⁸ and children,³⁹ EO does not appear to limit life expectancy nor is it associated with any increased risk of premalignant/malignant conditions. Nevertheless, the disease has a significant impact on quality of life.⁴⁰ In children, most will have recurring symptoms after withdrawal of medical treatment; however, dietary treatment can be highly successful in inducing and maintaining remission.³⁹ In adults, one-third of patients experience stable symptoms whereas one-quarter

have increasing dysphagia, when followed for some 7 years (range 1.4–11.5 years).³⁶ Any natural progression of disease from childhood to adult life has not been studied. Given the chronic nature of EO, affected children likely will continue to experience it into adulthood. This would support the epidemiological evidence showing a rise in prevalence over time.²⁸

Clinical characteristics and diagnostic criteria

The diagnosis depends on the clinical presentation, endoscopic features and histological criteria.⁴¹ The most common clinical presentation in adults is chronic, non-progressive dysphagia for solids (approximately 70%) and/or food impaction, followed by gastro-oesophageal reflux disease/heartburn (GORD, 38%) (table 2).³⁰ Vomiting and regurgitation may also be present. Uncommon are haematemesis, weight loss and failure to thrive. Children more often present with heartburn (38%), abdominal pain (31%), and failure to thrive compared to adults. Atopy (asthma, atopic dermatitis, eczema and food and seasonal allergies) is common in both children and adults.

Endoscopic features can be characteristic (table 3, fig 4A–D). Oesophageal furrows may indicate active disease; adherent white papules represent eosinophilic aggregates.⁴² Yet, no single endoscopic feature is pathognomonic for EO. In patients with endoscopic features of the disease, about one-third (8/21 in a recent report) will fulfil the diagnostic histological criteria.⁴³ Conversely, a normal endoscopy does not necessarily exclude it. Approximately 10% of adult patients with dysphagia and a normal endoscopic appearance will have it histologically.⁴³ One-third of children with severe histological eosinophilia have a normal oesophagus on endoscopy.³⁹

Table 1 Differential diagnosis for eosinophilic oesophagitis

Disorder	Feature
Primary	Primary eosinophilic oesophagitis ▶ atopic ▶ non-atopic ▶ familial
Secondary: eosinophilic related	Hypereosinophilic syndrome Eosinophilic gastroenteritis
Secondary: non-eosinophilic related	Gastro-oesophageal reflux disease Recurrent vomiting Infection (parasites such as helminths and fungi) Crohn's disease Oesophageal gastrointestinal stromal tumour Myeloproliferative disorders Carcinomatosis Allergic vasculitis Connective tissue diseases (scleroderma) Drugs/iatrogenic

Primary (idiopathic) disorders are those in which no other inciting cause is known. Secondary disorders are inflammatory, infectious or hypersensitivity illnesses which result in oesophageal eosinophilia.

Clinical practice points for eosinophilic oesophagitis

- ▶ Eosinophilic oesophagitis is an important and established cause of dysphagia
- ▶ Adult patients often present with dysphagia, food impaction, or reflux symptoms non-responsive to proton pump inhibitor therapy
- ▶ Endoscopic features are typical and need to be recognised; normal endoscopy does not exclude eosinophilic oesophagitis
- ▶ Biopsy for histology is critical for the diagnosis of eosinophilic oesophagitis: four to five biopsies in the mid-to upper oesophagus maximises sensitivity
- ▶ Topical corticosteroid is first-line treatment in adults; relapse is common
- ▶ Dilatation may be useful to treat fixed strictures after medical therapy, but is associated with an increased risk of mucosal lacerations and perforation
- ▶ Endoscopic complications may be as high as 31%

As histology is critical for the diagnosis of EO, biopsies should be attained regardless of the endoscopic appearance of the oesophagus.⁴¹ Biopsies might also be attained from the stomach and duodenum to rule out eosinophilic gastroenteritis and Crohn's disease.⁴¹ Although the literature varies widely on the threshold number of eosinophils per high-power field (ranging from 15 to 30 per high-power field (hpf)), consensus opinion suggests a diagnostic threshold number of ≥ 15 eosinophils/hpf in the mid oesophagus (table 4).⁴¹ On average, most patients will have >40 eosinophils/hpf.²⁴ There is no definite cut-off criterion to distinguish EO from acid-peptic gastro-oesophageal reflux solely based

on number of eosinophils, although reflux typically induces infiltrates with counts less than 10 per hpf.²⁴ Other supporting features of the disease include basal zone hyperplasia, increased papillary size, superficial eosinophilic layering/aggregates, and microabscesses. The sensitivity of biopsies for the diagnosis of EO depends on the number of biopsies taken, increasing from 55% for one biopsy specimen to 100% for five specimens.⁴⁴ Because acid-pepsin injury to the oesophagus causes a modest infiltration of eosinophils, some overlap can exist between EO and GORD, supporting the notion of doing proximal oesophageal biopsies to better distinguish EO. Thus all diagnostic features should be correlated with the clinical context.

Table 2 Clinical features of eosinophilic oesophagitis

	Adult	Paediatric (age dependent)
Common	Intermittent dysphagia (29–100%)	GORD-like symptoms (38%):
	Food impaction/foreign body (25–100%)	▶ Heartburn
	GORD-like symptoms (quite variable)	▶ Regurgitation
	▶ Nausea/vomiting	
	▶ Not responsive to PPIs	
	▶ Regurgitation	Abdominal pain (31%)
	▶ Heartburn	Nausea/vomiting
	▶ Not responsive to PPIs	Feeding intolerance/refusal
	Oesophageal stricture	Failure to thrive
	Food allergy	Food allergy
Uncommon	Haematemesis	Dysphagia
	Globus	Food impaction
	Water brash	Chest pain
	Weight loss	Diarrhoea
	Chest pain	
	Abdominal pain	
	Diarrhoea	
Associated conditions	History of atopy	Asthma
	Asthma	Allergic rhinitis
	Allergic rhinitis	Eczema
		Atopic dermatitis
		Family history of atopy

A wide range of symptoms have been reported for eosinophilic oesophagitis. In the paediatric population, presenting symptoms may be age-related (eg, young children may not be able to describe dysphagia or heartburn).

This table is modified from Yan and Shaffer,²¹ with permission from the publishers.

GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

Pathophysiology

The basis for developing EO is only partially understood.²⁰ Compared to other regions of the gastrointestinal tract, the oesophagus normally lacks eosinophils. Allergic responses, tissue injury or infection cause the trafficking of eosinophils to the oesophagus where they become activated to secrete chemokines, cytokines, lipid mediators and cytotoxic secretory products (see preceding sections). How this results in dysphagia and food impaction is unknown. The chronic inflammation likely causes thickening of the mucosa/submucosa and muscularis propria layers, leading to fibrosis and remodelling, according to endoscopic ultrasound case reports in children and adults.^{45–47} Collagen accumulates in the mucosa and lamina propria of the oesophagus while the basal layer thickens.⁴⁸ Oesophageal manometry varies in adults and children, but may be abnormal in one-half.^{41 49 50} Most of the positive findings are non-specific peristaltic abnormalities; however, high-amplitude contractions, spasms, tertiary contractions and aperistalsis have been reported.⁴⁹ Primary motility disorders are rare, having been identified in only 12 patients: two with achalasia, seven with diffuse oesophageal spasm, and three with the nutcracker oesophagus.⁴⁹ The authors also have another with scleroderma (personal communications). The mechanisms by which dysmotility

Table 3 Endoscopic features of eosinophilic oesophagitis

Endoscopic feature	Description
Feline oesophagus (corrugated or ringed oesophagus)	▶ Multiple concentric rings – fine or coarse – transient or fixed – web-like
Small calibre oesophagus	▶ Narrow, fixed internal diameter ▶ Featureless, unchanging column ▶ Poor expansion on air insufflation ▶ Proximal and/or distal stenosis or rings (appearance of Schatzki's ring)
Adherent white papules or exudates	▶ White exudates 1–2 mm in diameter which do not wash off (similar to candidiasis) ▶ Speckled patches ▶ Granular ▶ Vesicles ▶ Loss of vascular pattern
Linear oesophageal furrows	▶ Vertical oesophageal lines
Crêpe paper mucosa	▶ Fragile oesophageal mucosa ▶ Delicate, inelastic ▶ Mucosal abrasions or laceration with minimal contact

This table is modified from Yan and Shaffer,²¹ with permission from the publishers.

arises is not completely understood. Theories abound: increased contraction of fibroblasts in the presence of eosinophils, axonal necrosis from eosinophil degranulation, major basic protein effects on smooth muscle contraction, and inflammatory cytokine inhibition of acetylcholine release leading to dysmotility. The lower oesophageal sphincter pressure is normal in most patients; hypotensive and hypertensive lower oesophageal sphincter pressures are rarely seen. Some confusion arises because patients with EO may have concomitant GORD, based on pH testing.⁵⁰

Treatment

Multiple therapeutic regimens have been used with varying success in both the paediatric and adult populations (table 5).⁴¹ Dietary restriction with either an elemental or elimination diet has been very successful in children with reported response rates up to 98%.^{39 51 52} Dietary studies in adults are limited, appearing only as abstracts.^{53 54} Corticosteroids have been used successfully to treat EO in both children and adults. Swallowed fluticasone is effective for clinical, endoscopic, histological and immunological improvement,^{50 55–59} although only one randomised, double-blind, placebo-controlled trial has been published. In this study, 50% of children achieved histological remission, compared to 9% for placebo.⁵⁷ Approximately 75% of adults attained complete remission in non-randomised clinical studies.⁴¹ Recommended dosage is fluticasone 880–1760 µg per day split into twice or four times daily dosing for 6–8 weeks. Recurrence of symptoms is common and can occur in 50–60% at 1 year.^{41 55} Furthermore, up to 20%

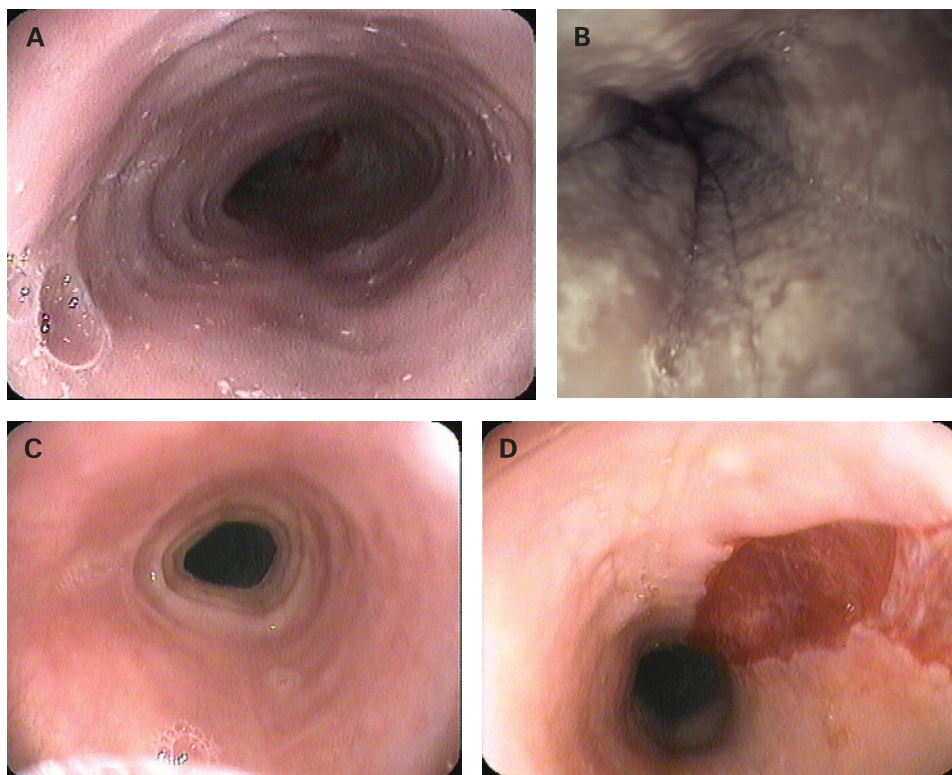
may develop oral and/or oesophageal candidiasis. Use of systemic steroids has only been published in the paediatric population; a 4 week regimen of 1.5 mg/kg methylprednisolone may be effective.⁶⁰ In a trial comparing topical fluticasone to oral prednisone, no significant difference was found in efficacy or relapse, although fewer adverse events were noted for fluticasone.⁶¹ Oral budesonide theoretically is a less cumbersome method of topical therapy than swallowing aerosolised particles. In a retrospective review of 20 children with EO, oral viscous budesonide 1–2 mg daily for 3–4 months resulted in an 80% response rate (defined as eosinophils <7/hpf) with a significant correlation between symptomatic, histological and endoscopic scores.⁴⁹ In a preliminary report in adults with the disease, 2 mg/day budesonide for 15 days produced remission (defined as <5 eosinophils/hpf) in 11/18 (61%), compared to 1/18 (5.7%) receiving placebo.⁶²

Other therapies for EO have employed small trials. Montelukast, a selective inhibitor of the LTD4 receptor, provided symptomatic improvement in eight adult patients with dysphagia secondary to EO.⁶³ Six patients, however, experienced recurrence of symptoms within 3 weeks of dose reduction or cessation. Further, treatment did not change the density of eosinophils on repeat biopsy. Mepolizumab, a humanised anti-IL5 monoclonal antibody, shown benefit in five patients without serious side effects.^{64 65} Specific eotaxin inhibitors are also under development.⁶⁶ Medications successfully used in eosinophilic gastroenteritis such as cromolyn and ketotifen (mast cell stabilising medications), and suplatast tosilate (a selective Th2 IL4 and IL5 inhibitor) have not been studied in adults with eosinophilic oesophagitis. Cromolyn was not efficacious in children with EO.³⁹ Dilatation is useful in symptomatic patients with fixed strictures, but because of the increased risk of causing a mucosal laceration or perforation, such manipulation should only be undertaken after a trial of medical treatment.

Complications

EO carries a relatively high endoscopic risk as either perforations or mucosal lacerations (fig 4D) from oesophageal dilatation, biopsy or even from simply passing an endoscope.^{36 38 68–70} Eight perforations have been reported in the literature – five were procedure-related,^{69 71 72} and three were spontaneous oesophageal ruptures (Boerhaave's syndrome).^{71–73} In a single-centre audit over a 5 year period, 11 of 36 patients (31%) with EO experienced complications: seven mucosal lacerations, three perforations, and one spontaneous emesis-induced rupture.⁷¹ The presence of strictures, a longer duration of symptoms, and higher density of eosinophilic infiltration were associated with an increased risk for complications. Dilation was involved in six of the complications, occurring with through-the-scope balloons in four, a bougie in one, and an endoscope as dilator in another. The perforation rate for food bolus removal requiring

Figure 4 Endoscopic images of eosinophilic oesophagitis. (A) Concentric rings, (B) linear furrows and adherent white exudates, (C) small calibre oesophagus with stricture, (D) mucosal laceration from diagnostic oesophago-gastroduodenoscopy.



rigid endoscopy has been reported at 2/134.⁷² At our centre, we have not observed such a high complication rate, with only 5.5% rate of minor complications over a 4 year period (personal communication).

EOSINOPHILIC GASTROENTERITIS

Eosinophilic gastritis and eosinophilic enteritis appear to be disorders separate from eosinophilic oesophagitis. Eosinophils are constitutive inhabitants of the gastrointestinal outside of the oesophagus in the normal, healthy state. Therefore, diagnosis of idiopathic eosinophilic gastroenteritis is more difficult than when the oesophagus is involved. Disorders are best categorised into primary (idiopathic) or secondary eosinophilic gastroenteritis (table 6). Primary eosinophilic gastroenteritis (EGE) has also been termed *allergic gastroenteropathy*, as a subset of patients have an

associated allergic component.^{74–76} Although considered idiopathic, an allergic mechanism may be involved as most patients exhibit increased total IgE and food-specific IgE levels. Secondary disorders linked to EGE include the hypereosinophilic syndrome (HES), coeliac disease, Crohn's disease, vasculitis (Churg–Strauss syndrome, polyarteritis nodosa), connective tissue disease (scleroderma), infection (*Helicobacter pylori*, parasites) and drug injury/hypersensitivity.

Epidemiology

EGE is exceedingly rare, lacking epidemiological data to estimate its true frequency. Since its original description in 1937,⁷⁷ fewer than 300 cases have been reported in the literature.^{42 75 78} Major referral centres may identify 1 case per 100 000 patients. Even the Mayo Clinic (from medical records documenting more than 4 million individuals) was only able to identify 40 patients with EGE from 1950 to 1987.⁷⁹ It can affect any age group, but the peak incidence is in third to fifth decade of life. There is a slight male predominance of about 1.4:1. EGE is a benign disorder, albeit the natural course of the disease is unknown.

Clinical presentation

Clinical feature of EGE are listed in table 7. The Klein classification⁸⁰ separates EGE into mucosal, muscular or (sub)serosal disease as the clinical presentation is dependent on the involved layer of the gastrointestinal tract.^{9 42 75 79 81} Approximately 57.5% have mucosal, 30% muscular and 12.5% (sub)serosal disease, respectively.⁷⁹ Patients with

Table 4 Histopathology of eosinophilic oesophagitis

	GORD	Eosinophilic oesophagitis
Eosinophilic infiltration (squamous epithelium)	<10/hpf	>15/hpf (peak count)
Other features	▶ Oesophagitis (usually distal) ▶ Intestinal metaplasia	▶ Oesophagitis (proximal and/or distal, may be patchy or segmental) ▶ Basal zone hyperplasia ▶ Increased papilla ▶ Superficial eosinophilic layering or aggregates ▶ Eosinophilic microabscesses

A minimum of >15 eosinophils in at least one high-power field ($\times 400$) is suggested for the diagnosis of eosinophilic oesophagitis.⁴¹ No definite cut-off criterion distinguishes eosinophilic oesophagitis from gastro-oesophageal reflux based solely on number of eosinophils.

This table is modified from Yan and Shaffer,²¹ with permission from the publishers.

GORD, gastro-oesophageal reflux disease; hpf, high-power field.

Recent advances in clinical practice

Table 5 Treatment regimens for eosinophilic oesophagitis

Treatment option	Protocol
Dietary therapy	► Avoidance of allergen depending on results of food allergy testing ► Six food elimination diet: milk, wheat, soy, egg, nuts, seafood ► Oligoantigenic diet: eliminate large number of suspected foods and allow limited nutritionally balanced diet ► Elemental diet: various formulas such as Neocate (free amino acids, corn syrup solids, medium chain triglycerides)
Topical corticosteroids	► Fluticasone swallowed in divided doses: – children: 440–880 µg/day ×6–8 weeks – adolescents/adult: 880–1760 µg/day ×6–8 weeks ► No spacer ► No food or drink for at least 30 min after ingesting the dose
Systemic (oral) corticosteroids	► Methylprednisolone 1.5 mg/kg/day (or equivalent dose prednisone) – divide into twice daily dosing ×4 weeks then taper over 6 weeks ► Budesonide – children: 1–2 mg daily ×3–4 months – adults*: 2–12 mg daily ×2–6 weeks
Montelukast	► Initial dose: 10 mg, orally, daily ► Titration: dose up to 100 mg/day depending on symptoms and tolerance ► Maintenance: once symptoms relieved titrate down to minimal dose to maintain remission (usually 20–40 mg/day)
Mepolizumab	► 10 mg/kg intravenous infusion every 4 weeks ×3 doses

*Presented in abstract form only.^{62 67}This table is modified from Yan and Shaffer,²¹ with permission from the publishers.

predominant mucosal disease present with symptoms similar to inflammatory bowel disease. This may include vomiting, abdominal pain, diarrhoea, gastrointestinal bleeding, iron deficiency anaemia, malabsorption, protein-losing enteropathy, or failure to thrive. Disease involving the muscularis propria typically presents with obstructive symptoms.⁸² Distinguishing features of serosal involvement are the presence of ascites (with a low serum:ascites albumin gradient), bloating, a high peripheral eosinophil count, and possibly features of peritonitis.^{79 83 84}

Diagnosis

The diagnosis of EGE may be elusive. Symptoms are non-specific. Peripheral eosinophilia is variable; the eosinophil count is normal in 25% of patients.⁷⁹ Atopy and allergies are associated in 25–75% of cases.⁷⁵ Radiographic studies help detect the muscular disease by finding stenosis or thickening of the stomach and small bowel folds.⁸⁵

Mucosal disease is the most readily diagnosed form of EGE, given that endoscopy can directly visualise any mucosal changes and acquire biopsies. Endoscopic features are nevertheless rather non-specific: thickened folds, erythema, friability, nodularity, and abnormal peristalsis.⁸⁶ Biopsies show increased eosinophils; however, no standards of diagnosis have been established. Indeed, the “normal” number of eosinophils has not been defined and criteria may differ between pathology departments. For example, the “normal” ileum may show as many as 30 eosinophils per high-power field.⁸⁷ Other suggestive histological features include eosinophilic infiltration of intestinal crypts and gastric glands. Other organs are not involved. Secondary causes of tissue eosinophilia,

like helminthic infestations, should be excluded. In the muscular form, endoscopy may appear normal, although a case report has been published on a non-healing gastric ulcer ultimately being diagnosed as the mural form of eosinophilic gastritis on surgical pathology.⁸⁸

Most EGE cases have been diagnosed on surgical, full-thickness biopsy or resection performed for obstruction or suspicion of malignancy. Serosal disease may be identified as part of an evaluation for ascites. Laparoscopy may reveal thickening of the peritoneum (both parietal and visceral) and white nodules; serosal biopsies are essential for the diagnosis.⁸³ Other causes, such as malignancy or tuberculosis, must be excluded.

Treatment

The rarity of EGE has limited any large prospective randomised therapeutic trials. The mainstay of treatment in non-obstructive disease is corticosteroid therapy.^{78 79 89} Prednisone at a dose of 20–40 mg daily for 8 weeks can yield a good response. Budesonide is an alternative steroid with fewer systemic side effects.⁹⁰ Those with serosal disease appear to experience the greatest response to corticosteroids.⁷⁹ Elimination or elemental diets may be helpful in patients with mucosal disease or identified allergic response to foods.^{91 92} Other therapies used with some success include cromolyn,^{93 94} montelukast,^{95 96} ketotifen,^{97 98} suplatast tosilate,⁹⁹ and octreotide.¹⁰⁰ When therapy ends, the disease tends to relapse. Therefore, steroid-sparing treatments, such as dietary modification or montelukast, are preferred maintenance strategies. Immunosuppressive agents, like azathioprine or mycophenolate mofetil, might prove to be alternatives to corticosteroids though clinical trials are lacking.

EOSINOPHILIC COLITIS

Eosinophilic colitis (EC) can also be categorised as either being primary (idiopathic) or secondary to other disorders (with a similar differential diagnosis as EGE, table 6). Primary EC (also known as *allergic colitis of infancy* or *dietary protein-induced proctocolitis of infancy syndrome*) is sub-classified into atopic and non-atopic variants. EC has a bimodal age distribution, usually affecting infants (mean age of 60 days) and adolescents.^{101 102} In contrast to EGE, most EC is thought to be non-IgE based, although the exact immunological mechanism is not fully understood. It may be an early expression of protein-induced enterocolitis of which cow's milk and soy proteins are considered the main culprits.^{103 104} EC may occur more often in infants who are exclusively breast-fed.^{101 105} It also may develop in children following solid organ transplantation. In one report, 37% of children with liver transplants on immunosuppression with tacrolimus had EC on rectal biopsy, performed to detect if lymphoproliferative disease had developed. Half of those with EC also had an atopic variant with elevated food specific IgE levels.¹⁰⁵

Table 6 Differential diagnosis for eosinophilic gastroenteritis and colitis

Disorder	Feature
Primary	Primary eosinophilic gastroenteritis
	▶ mucosal
	▶ muscularis
	▶ (sub)serosal
	Primary eosinophilic colitis
Secondary: eosinophilic related	▶ atopic
	▶ non-atopic
	Hypereosinophilic syndrome
	Protein hypersensitivity enteropathy
	Inflammatory bowel disease
	Celiac disease
	Infection (<i>Helicobacter pylori</i> , tuberculosis, parasites such as helminths and fungi, <i>Clostridium difficile</i> , <i>Shigella</i> , <i>Escherichia coli</i>)
	Lymphangiectasia
	Lymphoma/carcinoma
	Connective tissue disease (scleroderma)
Secondary: non-eosinophilic related	Vasculitis (polyarteritis nodosa, Churg–Strauss)
	Graft versus host disease
	Systemic mastocytosis
	Drugs/iatrogenic

A single case report has been published of an adult patient developing EC following bone marrow transplantation for acute myeloid leukaemia.¹⁰⁶

The clinical features of EC are similar to EGE depending on degree and location of colon involvement.^{9 101 107} Diarrhoea, which can be bloody,¹⁰⁸ is the classic presentation. Abdominal pain, anorexia and weight loss are other features, although the majority of infants are otherwise healthy with no constitutional features. Obstructive presentations (like caecal volvulus or intussusception) seem to be more common in adults compared to children.^{109 110} EC can even masquerade as a tumour.^{111–113} Laboratory features include increased peripheral blood eosinophilia or eosinophils on stool examination.

Endoscopic findings are non-specific, being similar to EGE if the mucosa is involved: erythema, loss of vascularity, friability, nodularity and lymphonodular hyperplasia. Histology reveals increased eosinophils and aggregates of eosinophils in the lamina propria, muscularis propria, or subserosa. Other inflammatory cells are not present. The architecture of the mucosa is generally preserved, helping to distinguish EC from other colitides.

In infants, the clinical course is usually benign. Withdrawal of the culprit protein trigger(s) usually resolves any symptoms. Bloody diarrhoea typically disappears within 72 h. Most infants will be able to tolerate a subsequent re-introduction of the culprit protein by age 1–3 years.^{101 103} Controversy exists as to whether or not infantile EC predisposes to the future development of inflammatory bowel disease.¹⁰¹

Older patients (adolescents and adults) may require medications because IgE-associated triggers are rarely identified even in the atopic variant.⁹ Although well-designed clinical trials are lacking, short courses of topical or systemic corticosteroids (prednisone 20–40 mg or budesonide 9 mg daily) for 1–2 weeks or a 5-aminosalicylic acid appear to be efficacious. The effectiveness of other agents used in EGE is unknown. In refractory cases, immunomodulator therapy with azathioprine may be required. The natural history of eosinophilic colitis in older patients is unknown; it tends to follow a waxing and waning course similar to eosinophilic oesophagitis and eosinophilic gastroenteritis.

CONCLUSION

Primary eosinophilic gastrointestinal disorders have undergone a renewed interest in the past decade. Eosinophilic oesophagitis has become a well-recognised cause of dysphagia and likely is the main cause of food bolus obstruction in young otherwise healthy adult men. This entity is

Table 7 Clinical features of eosinophilic gastroenteritis

Layer of involvement	Distribution ⁷⁹ (%)	Symptom	Radiology ⁸⁵
Mucosal	57.5	Nausea/vomiting	Fold thickening
		Abdominal pain	Polyps
		Diarrhoea	Ulceration
		Gastrointestinal bleeding/anaemia	Luminal narrowing
		Malabsorption	Hypersecretion
		Protein-losing enteropathy	Irritability
		Failure to thrive	Spasm
		Symptoms of luminal obstruction	Stenosis
Muscularis propria	30		Rigidity
			Dysmotility
			Any of the findings in predominant mucosal disease
			Eosinophilic ascites
(Sub)Serosal	12.5	Ascites	Adherent loops of bowel
		Bloating	Thicken omentum and mesentery
		High peripheral eosinophilia	Eosinophilic lymphadenopathy
		Peritonitis	Eosinophilic pleural effusion
			Any of the findings in predominant mucosal and/or muscularis disease

Clinical practice points for eosinophilic gastroenteritis

- ▶ Eosinophilic gastroenteritis is a rare disease; secondary disorders must be excluded
- ▶ Clinical presentation is influenced by the layer of gut involved:
 - mucosal: pain, diarrhea, malabsorption
 - muscularis: obstruction
 - serosal: ascites, bloating, tends to have higher peripheral eosinophilia
- ▶ Endoscopic features (non-specific) accompany mucosal disease; muscularis and serosal disease are diagnosed on surgical full thickness biopsy or resection
- ▶ The mainstay of therapy is corticosteroids
- ▶ Relapse is common; steroid sparing alternatives should be considered in those with severe cases, which are steroid dependent or refractory
- ▶ The natural history is unknown

Clinical practice points for eosinophilic colitis

- ▶ Eosinophilic colitis is a rare disease; secondary disorders must be excluded
- ▶ The disease is the most common cause of bloody stools in the first year of life:
 - withdrawal of the offending protein trigger usually results in clinical improvement
 - prognosis is very good; triggering foods can be re-introduced later by age 1–3 years
- ▶ Older children and adults with eosinophilic colitis typically present with diarrhoea and abdominal pain
 - symptoms are dependent on location and degree of colon involved
 - treatment is withdrawal of offending food if atopic variant
 - a short course of corticosteroid (prednisone 20–40 mg daily for 1–2 weeks) or a 5-aminosalicylic acid is usually required
- ▶ Endoscopy may be normal or have non-specific features of inflammation; histology shows an increased infiltration of eosinophils or focal aggregates
- ▶ Older patients with the disease have a relapsing course; steroid-sparing alternatives should be considered in severe cases that are steroid-dependent or refractory
- ▶ The natural history is unknown

separate from eosinophilic gastroenterocolitis and is increasing in incidence. Recognition of its clinical presentation along with endoscopic and histological features provides the correct diagnosis and subsequent treatment. Eosinophilic gastroenteritis and colitis are quite rare but must be included in the differential diagnosis of non-specific gastrointestinal symptoms. Increased knowledge of the

pathophysiology and underlying immune mechanisms should lead to more effective management of disorders of eosinophils. Under active investigation are agents to specifically block IL5, eotaxins or their receptors. Many questions remain unanswered: given the waxing and waning course of disease, what are the treatment goals and endpoints? Is there a role for maintenance therapy? What is the natural history of the disorders and does treatment alter the natural history? Vigorous randomised, controlled trials assessing current (and any novel) therapies are necessary to determine which agents are most effective. Eosinophils have always been a component of gastrointestinal tract physiology; our understanding of their role(s) has only just begun.

Competing interests: None.

REFERENCES

1. **Warren DJ**, Moore MA. Synergism among interleukin 1, interleukin 3, and interleukin 5 in the production of eosinophils from primitive hemopoietic stem cells. *J Immunol* 1988;**140**:94–9.
2. **Yamaguchi Y**, Hayashi Y, Sugama Y, *et al*. Highly purified murine interleukin 5 (IL-5) stimulates eosinophil function and prolongs in vitro survival. IL-5 as an eosinophil chemotactic factor. *J Exp Med* 1988;**167**:1737–42.
3. **Yamaguchi Y**, Suda T, Suda J, *et al*. Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors. *J Exp Med* 1988;**167**:43–56.
4. **Dent LA**, Strath M, Mellor AL, *et al*. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990;**172**:1425–31.
5. **Mishra A**, Hogan SP, Lee JJ, *et al*. Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 1999;**103**:1719–27.
6. **Kato M**, Kephart GM, Talley NJ, *et al*. Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec* 1998;**252**:418–25.
7. **Rothenberg ME**, Mishra A, Brandt EB, *et al*. Gastrointestinal eosinophils in health and disease. *Adv Immunol* 2001;**78**:291–328.
8. **Rothenberg ME**, Luster AD, Lilly CM, *et al*. Constitutive and allergen-induced expression of eotaxin mRNA in the guinea pig lung. *J Exp Med* 1995;**181**:1211–6.
9. **Rothenberg ME**. Eosinophilic gastrointestinal disorders. *J Allergy Clin Immunol* 2004;**113**:11–28.
10. **Garcia-Zepeda EA**, Rothenberg ME, Ownbey RT, *et al*. Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. *Nat Med* 1996;**2**:449–56.
11. **Ponath PD**, Qin S, Ringler DJ, *et al*. Cloning of the human eosinophil chemoattractant, eotaxin -- expression, receptor binding, and functional properties suggest a mechanism for the selective recruitment of eosinophils. *J Clin Invest* 1996;**97**:604–12.
12. **Forssmann U**, Ugucioni M, Loetscher P, *et al*. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 1997;**185**:2171–6.
13. **Shinkai A**, Yoshisue H, Koike M, *et al*. A novel human CC chemokine, eotaxin-3, which is expressed in IL-4-stimulated vascular endothelial cells, exhibits potent activity toward eosinophils. *J Immunol* 1999;**163**:1602–10.
14. **Rothenberg ME**, Luster AD, Leder P. Murine eotaxin: an eosinophil chemoattractant inducible in endothelial cells and in interleukin 4-induced tumor suppression. *Proc Natl Acad Sci U S A* 1995;**92**:8960–4.
15. **Matthews AN**, Friend DS, Zimmermann N, *et al*. Eotaxin is required for the baseline level of tissue eosinophils. *Proc Natl Acad Sci U S A* 1998;**95**:6273–8.
16. **Gurish MF**, Humbles A, Tao H, *et al*. CCR3 is required for tissue eosinophilia and larval cytotoxicity after infection with *Trichinella spiralis*. *J Immunol* 2002;**168**:5730–6.
17. **Bochner BS**, Klunk DA, Sterbinsky SA, *et al*. IL-13 selectively induces vascular cell adhesion molecule-1 expression in human endothelial cells. *J Immunol* 1995;**154**:799–803.
18. **Bochner BS**, Schleimer RP. The role of adhesion molecules in human eosinophil and basophil recruitment. *J Allergy Clin Immunol* 1994;**94**:427–38; quiz 39.

19. **Dobbins JW**, Sheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. *Gastroenterology* 1977;**72**:1312–6.
20. **Ferguson DD**, Foxx-Orenstein AE. Eosinophilic esophagitis: an update. *Dis Esophagus* 2007;**20**:2–8.
21. **Yan BM**, Shaffer EA. Eosinophilic esophagitis: a newly established cause of dysphagia. *World J Gastroenterol* 2006;**12**:2328–34.
22. **Winter HS**, Madara JL, Stafford RJ, *et al*. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology* 1982;**83**:818–23.
23. **Blanchard C**, Wang N, Rothenberg ME. Eosinophilic esophagitis: pathogenesis, genetics, and therapy. *J Allergy Clin Immunol* 2006;**118**:1054–9.
24. **Parfitt JR**, Gregor JC, Suskin NG, *et al*. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. *Mod Pathol* 2006;**19**:90–6.
25. **Noel RJ**, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;**351**:940–1.
26. **Esposito S**, Marinello D, Paracchini R, *et al*. Long-term follow-up of symptoms and peripheral eosinophil counts in seven children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2004;**38**:452–6.
27. **Zink DA**, Amin M, Gebara S, *et al*. Familial dysphagia and eosinophilia. *Gastrointest Endosc* 2007;**65**:330–4.
28. **Straumann A**, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;**115**:418–9.
29. **Williams CI**, Dupre MP, Kaplan GG, *et al*. Rising incidence of eosinophilic esophagitis in the Calgary Health Region: A population based study. *Gastroenterology* 2008;**134**:A–291.
30. **Kapel RC**, Miller JK, Torres C, *et al*. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008;**134**:1316–21.
31. **Desai TK**, Stecevic V, Chang CH, *et al*. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc* 2005;**61**:795–801.
32. **Kerlin P**, Jones D, Remedios M, *et al*. Prevalence of eosinophilic esophagitis in adults with food bolus obstruction of the esophagus. *J Clin Gastroenterol* 2007;**41**:356–61.
33. **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**:615–20.
34. **Vanderheyden AD**, Petras RE, DeYoung BR, *et al*. Emerging eosinophilic (allergic) esophagitis: increased incidence or increased recognition? *Arch Pathol Lab Med* 2007;**131**:777–9.
35. **Prasad G**, Smyrk TC, Schleck C, *et al*. Seasonal variation in the incidence of eosinophilic esophagitis over 30 years: A population based study. *Gastroenterology* 2008;**134**:A–619.
36. **Straumann A**, Spichtin HP, Grize L, *et al*. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;**125**:1660–9.
37. **Potter JW**, Saeian K, Staff D, *et al*. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. *Gastrointest Endosc* 2004;**59**:355–61.
38. **Croese J**, Fairley SK, Masson JW, *et al*. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc* 2003;**58**:516–22.
39. **Liacouras CA**, Spergel JM, Ruchelli E, *et al*. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;**3**:1198–206.
40. **Straumann A**. The natural history and complications of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;**18**:99–118; ix.
41. **Furuta GT**, Liacouras CA, Collins MH, *et al*. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;**133**:1342–63.
42. **Straumann A**, Simon HU. The physiological and pathophysiological roles of eosinophils in the gastrointestinal tract. *Allergy* 2004;**59**:15–25.
43. **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**:2627–32.
44. **Gonsalves N**, Policarpo-Nicolas M, Zhang Q, *et al*. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;**64**:313–9.
45. **Fox VL**, Nurko S, Teitelbaum JE, *et al*. High-resolution EUS in children with eosinophilic “allergic” esophagitis. *Gastrointest Endosc* 2003;**57**:30–6.
46. **Furuta K**, Adachi K, Kowari K, *et al*. A Japanese case of eosinophilic esophagitis. *J Gastroenterol* 2006;**41**:706–10.
47. **Stevoff C**, Rao S, Parsons W, *et al*. EUS and histopathologic correlates in eosinophilic esophagitis. *Gastrointest Endosc* 2001;**54**:373–7.
48. **Mishra A**, Wang M, Pemmaraju VR, *et al*. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology* 2008;**134**:204–14.
49. **Nurko S**, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;**18**:73–89; ix.
50. **Remedios M**, Campbell C, Jones DM, *et al*. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* 2006;**63**:3–12.
51. **Kagalwalla AF**, Sentongo TA, Ritz S, *et al*. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;**4**:1097–102.
52. **Kelly KJ**, Lazenby AJ, Rowe PC, *et al*. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;**109**:1503–12.
53. **Gonsalves N**, Yang GY, Doerfler B, *et al*. A prospective clinical trial of six food elimination diet and reintroduction of causative agents in adults with eosinophilic esophagitis. *Gastroenterology* 2008;**134**:A–104.
54. **Penfield JD**, Lang D, Ching EL, *et al*. Adults with eosinophilic esophagitis: What is the utility of routine allergy evaluation? *Gastroenterology* 2008;**134**:A–730.
55. **Arora AS**, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003;**78**:830–5.
56. **Faubion WA**, Jr., Perrault J, Burgart LJ, *et al*. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;**27**:90–3.
57. **Konikoff MR**, Noel RJ, Blanchard C, *et al*. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;**131**:1381–91.
58. **Noel RJ**, Putnam PE, Collins MH, *et al*. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;**2**:568–75.
59. **Teitelbaum JE**, Fox VL, Twarog FJ, *et al*. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002;**122**:1216–25.
60. **Liacouras CA**, Wenner WJ, Brown K, *et al*. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;**26**:380–5.
61. **Schaefer ET**, Fitzgerald JF, Molleston JP, *et al*. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008;**6**:165–73.
62. **Straumann A**, Degen L, Felder S, *et al*. Budesonide as induction treatment for active eosinophilic esophagitis in adolescents and adults: A randomized, double-blind, placebo-controlled study (Bee-I Trial). *Gastroenterology* 2008;**134**:A–104.
63. **Attwood SE**, Lewis CJ, Bronder CS, *et al*. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003;**52**:181–5.
64. **Garrett JK**, Jameson SC, Thomson B, *et al*. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;**113**:115–9.
65. **Stein ML**, Collins MH, Villanueva JM, *et al*. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;**118**:1312–9.
66. **Main S**, Handy R, Wilton J, *et al*. A potent human anti-eotaxin1 antibody, CAT-213: isolation by phage display and in vitro and in vivo efficacy. *J Pharmacol Exp Ther* 2006;**319**:1395–404.
67. **Karnam U**, Hirano I. Effectiveness of oral budesonide suspension in adult patients with eosinophilic esophagitis. *Gastroenterology* 2008;**134**:A–289.
68. **Eisenbach C**, Merle U, Schirmacher P, *et al*. Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis. *Endoscopy* 2006;**38**(Suppl 2):E43–4.
69. **Kaplan M**, Mutlu EA, Jakate S, *et al*. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. *Clin Gastroenterol Hepatol* 2003;**1**:433–7.
70. **Morrow JB**, Vargo JJ, Goldblum JR, *et al*. The ringed esophagus: histological features of GERD. *Am J Gastroenterol* 2001;**96**:984–9.
71. **Cohen MS**, Kaufman AB, Palazzo JP, *et al*. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2007;**5**:1149–53.
72. **Straumann A**, Bussmann C, Zuber M, *et al*. Eosinophilic esophagitis: analysis of food impaction and perforation in 251

- adolescent and adult patients. *Clin Gastroenterol Hepatol* 2008;**6**:598–600.
73. **Riou PJ**, Nicholson AG, Pastorino U. Esophageal rupture in a patient with idiopathic eosinophilic esophagitis. *Ann Thorac Surg* 1996;**62**:1854–6.
 74. **Bischoff S**, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. *Gastroenterology* 2005;**128**:1089–113.
 75. **Khan S**, Orenstein SR. Eosinophilic gastroenteritis: epidemiology, diagnosis and management. *Paediatr Drugs* 2002;**4**:563–70.
 76. **Ngo P**, Furuta G, Burks W. The pathobiology of eosinophilic gastroenteritis of childhood: is it really the eosinophil, allergic mediated, or something else? *Curr Gastroenterol Rep* 2004;**6**:436–40.
 77. **Kajiser R**. Zur kenntnis der allergischen affektionen des Verdauungskanal vom standpunkt des chirurgen aus. *Arch Klin Chir* 1937;**188**:36–64.
 78. **Naylor AR**. Eosinophilic gastroenteritis. *Scott Med J* 1990;**35**:163–5.
 79. **Talley NJ**, Shorter RG, Phillips SF, *et al*. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990;**31**:54–8.
 80. **Klein NC**, Hargrove RL, Sleisenger MH, *et al*. Eosinophilic gastroenteritis. *Medicine (Baltimore)* 1970;**49**:299–319.
 81. **Mendez-Sanchez N**, Chavez-Tapia NC, Vazquez-Elizondo G, *et al*. Eosinophilic gastroenteritis: a review. *Dig Dis Sci* 2007;**52**:2904–11.
 82. **Sacher P**. [Surgical aspects of eosinophilic gastroenteritis (author's translation)]. *Z Kinderchir* 1981;**34**:25–30.
 83. **Solis-Herruzo JA**, de Cuenca B, Munoz-Yague MT. Laparoscopic findings in serosal eosinophilic gastroenteritis. Report of two cases. *Endoscopy* 1988;**20**:152–3.
 84. **Tran D**, Salloum L, Tshibaka C, *et al*. Eosinophilic gastroenteritis mimicking acute appendicitis. *Am Surg* 2000;**66**:990–2.
 85. **Vitellas KM**, Bennett WF, Bova JG, *et al*. Radiographic manifestations of eosinophilic gastroenteritis. *Abdom Imaging* 1995;**20**:406–13.
 86. **Navab F**, Kleinman MS, Algazy K, *et al*. Endoscopic diagnosis of eosinophilic gastritis. *Gastrointest Endosc* 1972;**19**:67–9.
 87. **Lowichik A**, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 1996;**9**:110–4.
 88. **Scolapio JS**, DeVault K, Wolfe JT. Eosinophilic gastroenteritis presenting as a giant gastric ulcer. *Am J Gastroenterol* 1996;**91**:804–5.
 89. **Lee CM**, Changchien CS, Chen PC, *et al*. Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 1993;**88**:70–4.
 90. **Tan AC**, Kruimel JW, Naber TH. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. *Eur J Gastroenterol Hepatol* 2001;**13**:425–7.
 91. **Justinich C**, Katz A, Gurbindo C, *et al*. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996;**23**:81–5.
 92. **Leinbach GE**, Rubin CE. Eosinophilic gastroenteritis: a simple reaction to food allergens? *Gastroenterology* 1970;**59**:874–89.
 93. **Di Gioacchino M**, Pizzicannella G, Fini N, *et al*. Sodium cromoglycate in the treatment of eosinophilic gastroenteritis. *Allergy* 1990;**45**:161–6.
 94. **Perez-Millan A**, Martin-Lorente JL, Lopez-Morate A, *et al*. Subserosal eosinophilic gastroenteritis treated efficaciously with sodium cromoglycate. *Digestive Diseases and Sciences* 1997;**42**:342–4.
 95. **Neustrom MR**, Friesen C. Treatment of eosinophilic gastroenteritis with montelukast. *J Allergy Clin Immunol* 1999;**104**:506.
 96. **Quack I**, Sellin L, Buchner NJ, *et al*. Eosinophilic gastroenteritis in a young girl – long term remission under Montelukast. *BMC Gastroenterol* 2005;**5**:24.
 97. **Bolukbas FF**, Bolukbas C, Uzunkoy A, *et al*. A dramatic response to ketotifen in a case of eosinophilic gastroenteritis mimicking abdominal emergency. *Dig Dis Sci* 2004;**49**:1782–5.
 98. **Melamed I**, Feanny SJ, Sherman PM, *et al*. Benefit of ketotifen in patients with eosinophilic gastroenteritis. *Am J Med* 1991;**90**:310–4.
 99. **Shirai T**, Hashimoto D, Suzuki K, *et al*. Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J Allergy Clin Immunol* 2001;**107**:924–5.
 100. **Rausch T**, Gyr K, Wegmann W, *et al*. [Symptomatic therapy of severe diarrhea in eosinophilic gastroenteritis with the somatostatin analog octreotide (Sandostatin)]. *Schweiz Med Wochenschr Suppl* 1997;**89**:9S–13S.
 101. **Guajardo JR**, Rothenberg ME. Eosinophilic esophagitis, gastroenteritis, gastroenterocolitis, and colitis. In: Metcalfe DD, Sampson HA, Simon RA, eds. *Food Allergy: adverse reactions to foods and additives*. Malden, Massachusetts: Blackwell Publishing, 2003:217–26.
 102. **Odze RD**, Wershil BK, Leichtner AM, *et al*. Allergic colitis in infants. *J Pediatr* 1995;**126**:163–70.
 103. **Maloney J**, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE-mediated cow's milk allergy. *Pediatr Allergy Immunol* 2007;**18**:360–7.
 104. **Van Sickle GJ**, Powell GK, McDonald PJ, *et al*. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1985;**88**:1915–21.
 105. **Lee JH**, Park HY, Choe YH, *et al*. The development of eosinophilic colitis after liver transplantation in children. *Pediatr Transplant* 2007;**11**:518–23.
 106. **Ashida T**, Shimada T, Kawanishi K, *et al*. Eosinophilic colitis in a patient with acute myeloid leukemia after allogeneic bone marrow transplantation. *Int J Hematol* 2003;**78**:76–8.
 107. **Nielsen OH**, Vainer B, Rask-Madsen J. Non-IBD and noninfectious colitis. *Nat Clin Pract Gastroenterol Hepatol* 2008;**5**:28–39.
 108. **Ertugrul I**, Ulker A, Turhan N, *et al*. Eosinophilic colitis as an unusual cause of severe bloody diarrhea. *Turk J Gastroenterol* 2008;**19**:54–6.
 109. **Velchuru VR**, Khan MA, Hellquist HB, *et al*. Eosinophilic colitis. *J Gastrointest Surg* 2007;**11**:1373–5.
 110. **Box JC**, Tucker J, Watne AL, *et al*. Eosinophilic colitis presenting as a left-sided colocolonic intussusception with secondary large bowel obstruction: an uncommon entity with a rare presentation. *Am Surg* 1997;**63**:741–3.
 111. **Male PJ**, de Toledo F, Widgren S, *et al*. Pseudotumoral enterocolitis and massive eosinophilia. *Gut* 1983;**24**:345–50.
 112. **Losanoff JE**, Kjossev KT. Overwhelming eosinophilic gastroenterocolitis associated with intestinal obstruction and carcinoma of the colon. *Am J Gastroenterol* 1995;**90**:1030.
 113. **Lim K**, Black R. Eosinophilic colitis masquerading as colonic cancer. *Aust N Z J Surg* 2000;**70**:682–4.