

Eosinophilic Gastroenteritis

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Opinion statement

There are no evidence-based studies of the treatment of patients with eosinophilic gastroenteritis. Treatment decisions depend on experience gained from observations linking causative entities, principal clinical manifestations, and anticipated natural history of the disease. Because clinical symptoms and organ involvement probably vary with etiology, classification as to the likely cause (*eg*, food allergy or other dietary intolerance, idiosyncratic drug reaction, occult infection, idiopathic) determines the decisions made about dietary, pharmacologic, and surgical treatment. Elimination of foods and the use of elemental diets, corticosteroids, and mast cell inhibitors (*eg*, cromolyn sodium, ketotifen), alone or in combination, all have their place, depending on the age of the patient, organ involved, clinical presentation, and clinical urgency. Isolated cases are diagnosed only at surgical exploration for acute abdominal catastrophes; in these instances, further therapy depends on whether resection is done, but most patients remain in remission after surgery. Occult parasitism remains an elusive and unrecognized cause of an unknown number of cases, suggesting that empiric antihelminthic therapy should be tried in some patients. Individual reports of success with nonsystemic steroids and leukotriene inhibitors have been published.

Introduction

Eosinophilic gastroenteritis (EGE) is defined as gastrointestinal tissue eosinophilia associated with clinically meaningful digestive tract symptoms in the absence of obvious alternative cause, such as parasitic infection, classic inflammatory bowel disease, gastrointestinal or distant neoplasm, vasculitis, hypereosinophilic syndrome, and other causes. EGE has been reported in several hundred patients over six decades. About 50% of cases have some allergic association, such as atopic dermatitis, asthma or other airway allergy, or allergy to foods or drugs. From the earliest reports describing an intense gastric eosinophilic inflammatory response to drug or food sensitivity, the entity has evolved through several classification schemes, none of which are completely predictive of the therapeutic options [1]. Radiologic diagnosis with surgical confirmation was the rule until the endoscopic era, when a localized mucosal form was recognized and was separated from surgical cases causing obstruction or ascites. Emphasis on the features of allergic gastroenteropathy

(iron-deficiency anemia, diarrhea, weight loss, protein-losing enteropathy, malabsorption, food sensitivity) then dominated consideration [2]. Because of the poor results with dietary approaches in patients, corticosteroids remained the mainstay of therapy in most case reports and large collected series [3,4].

There are no controlled studies of any pharmacologic treatments advocated for EGE. Treatment decisions are based on anecdote, observation, and in some cases, longitudinal follow-up of small groups of patients whose pretreatment status is the only control. Under these circumstances, there have been five major developments in recent decades that impact decision making about therapy:

- Evidence that supports food hypersensitivity as a cause of EGE in some individuals, with unequivocal responses to elimination or elemental diets [5–8,9•].
- Observations that suggest that mast cell inhibitor therapy is effective and may be an alternative to steroid dependence in some patients [10–12].

- Recognition of eosinophilic esophagitis as a distinct but related entity, with evidence for food allergy versus gastroesophageal reflux disease (GERD), offering different treatment opportunities [13–19,20•,21,22•,23,24].
- Persistent reports of other cases worldwide, usually acute, that often require surgical therapy, in which no role for allergy can be demonstrated [25–29].
- Seminal observations that link occult parasitism to cases otherwise indistinguishable from idiopathic EGE [26,30•,31].

In addition, scattered individual case reports of success with nonsteroidal or nonsystemic steroid therapy have been published and are described in *Emerging therapies*.

Diet therapy generally was regarded as ineffective in individuals with EGE until well-studied individual case reports with comprehensive allergic evaluations showed otherwise. Longstanding disease in young adults attained remission following the dietary exclusion of milk [5] or beef [6]. Katz *et al.* [7] studied a group of young children with iron deficiency, protein-losing enteropathy, and EGE. On the basis of immunologic study and response to therapy, the authors distinguished between patients with milk-sensitive enteropathy (younger than 1 year, normal immunoglobulin E [IgE]) and EGE (later onset, atopy, IgE reactivity to milk and other foods). Though the first group responded to milk exclusion alone, elimination diet therapy was not effective in the children with multiple food allergies, who required corticosteroids for remission. An 18-year-old male with lifetime food allergy, EGE, and steroid dependence whose symptoms failed to respond to therapy with elimination diet and cromolyn became steroid-free and reversed growth failure when placed on an elemental diet [8]. Sicherer *et al.* [9•] recently studied 31 children (6 months to 17 years of age), including 17 with cow's milk allergy and 14 with EGE and multiple food allergies (*eg*, soy, egg, peanut, and other foods). The EGE group previously had not responded to milk exclusion or hydrolyzed formula diets. In contrast to the results of Katz *et al.* [7], this study showed that elemental diet therapy in both groups allowed normal growth for up to 40 months. In addition, there were significant reductions in percent eosinophilia and increases in iron and hemoglobin concentrations [9•]. Thus, in patients with well-characterized EGE in whom there is convincing evidence of an allergy to foods, the pathogenic role of allergy is further established by the response to elimination diet.

Oral administration of cromolyn sodium (disodium cromoglycate) and ketotifen, which are inhibitors of mast cell degranulation and are used for other allergic and eosinophilic conditions, has undergone some study in individuals with EGE. Several case reports have suggested a role for cromolyn in some steroid-dependent or steroid-resistant patients and other patient groups, but cromolyn failure also has been documented. A summary

of over 20 years of publications showed two series and a few individual reports of cases in which cromolyn therapy alone was effective [1]. In some of these reports, objective parameters of improvement included correction of anemia, hypoalbuminemia, and growth failure [10]. A smaller group of patients requiring steroids for remission could be maintained in a steroid-free state with cromolyn [11]. The typical responder was a young person with evidence for IgE-mediated food allergy and an incomplete response to dietary elimination [10,11]. Ketotifen, a drug with similar properties to cromolyn sodium that is not available in the United States, has been reported beneficial in one group of patients [12]. No further experience has been presented.

Eosinophilic esophagitis originally was described as a component of EGE [13]. Later endoscopic and radiologic series included individuals with isolated esophageal eosinophilia [14] in whom there was neither other organ eosinophilia nor evidence for GERD [15]. Intraepithelial eosinophilia as a marker of reflux esophagitis was first described in children [16]. More intense esophageal eosinophilia may be associated with multiple esophageal rings in children [17]. Cases in adults with similar gross and microscopic findings at endoscopy have been considered to be an expression of GERD [18,19]. Primary eosinophilic esophagitis as a separate entity in children has been well characterized and may involve only the esophagus or may be part of EGE [20•]. Evidence of food hypersensitivity, absence of pH manometric evidence for reflux, and failure of antireflux therapy characterize this group of patients, who account for 1% or more of children evaluated for reflux symptoms, and who respond to corticosteroids, dietary elimination, or elemental diet [21,22•,23]. A study of the diagnostic approach to this problem in infants showed that in patients younger than 1 year, cow's milk protein allergy is a major cause of GERD, and the clinical response to elimination of cow's milk is superior to antireflux therapy [24]. In this study, esophageal eosinophilia was not quantified between study groups, so the association with other studies of eosinophilic esophagitis is somewhat peripheral, as is the relationship to cow's milk protein allergic gastroenteropathy. Children with eosinophilic esophagitis should be investigated for food sensitivity and treated accordingly. Older patients may have either a variant form of reflux esophagitis or a disease in the spectrum of EGE.

Many individual case reports in recent years confirm that patients who meet diagnostic criteria for EGE occasionally present with various kinds of acute abdominal problems [25] as mimics of inflammatory bowel disease or intestinal tumor [26,27] or as variations of peptic ulcer disease or gastric outlet obstruction [28,29]. No new therapeutic or etiologic insights come from these isolated reports; they emphasize the protean nature of

disorders included in this diagnosis and the fact that some patients eventually are diagnosed only when surgically resected tissue is examined. Other patients require elective operation after failure of conventional and corticosteroid therapy; of this group, some experience remission following surgery, whereas others receive brief courses of corticosteroids with resolution.

Empiric antihelminthic therapy has been advocated in some circumstances because frequently no parasite can be identified in spite of multiple stool examinations and other studies [1,30]. Infections with *Ancylostoma*, *Enterobius*, *Eustoma*, *Toxocara*, *Strongyloides*, *Ascaris*, *Schistosoma*,

and *Trichuris* can mimic idiopathic EGE. In strongyloidiasis, empiric steroid therapy can lead to lethal systemic dissemination. Recent studies showing serologic evidence of *Ascaris* [26] or *Anisakis* [31] infection in individuals thought to have “idiopathic” EGE emphasizes the importance of considering occult parasitism in any patient without other likely causative associations.

Individual reports of sensitivity to gemfibrozil [32] and bee pollen [33] add to the long list of ingested agents capable of causing EGE [1]. The only treatment required for these forms is recognition, discontinuation of the agent, and avoidance.

Treatment

- The clinical dilemma represented by EGE is well summarized in the words of Kelly [34••]: “Can a 77-year-old woman with a 12-year history of intermittent cramping, epigastric pain, vomiting, a 30-lb weight loss, ankle-swelling edema, diarrhea, a 30% peripheral eosinophil count, and an eosinophilic infiltration of the small intestinal mucosa have the same disease process as a 25-day-old girl with a 1-week history of nonprojectile, nonbilious vomiting, pylorospasm, and eosinophilic infiltration of the lamina propria and submucosa of the gastric antrum?” Understanding of food allergy has progressed from the therapeutic nihilism of the past to a candidate explanation for several disorders, including EGE [35••]. Much remains to be learned about the pathophysiology of these and other disorders in the spectrum of EGE. Until controlled trials provide for better understanding of treatment, an algorithmic representation of a decision making approach to the therapy for patients with EGE is presented in Figure 1.

Diet and lifestyle

- Dietary exclusion of allergens as determined by formal allergy evaluation is helpful in selected patients. History, diet diary, elimination diet, skin tests, radioallergosorbent tests, and blinded food challenges all have a place in designing a food exclusion plan. Most patients are children or young adults with other forms of atopy. Men outnumber women by two to one in series of patients with allergic EGE.
- Elemental amino acid–based diets are useful in patients in whom multiple food allergies are found, both in isolated eosinophilic esophagitis refractory to antireflux therapy and in multiorgan EGE, if food exclusion fails.
- If the symptoms of food allergy improve after 2 to 4 weeks of elemental diet therapy, single foods are reintroduced every 3 to 5 days. The return of symptoms leads to the exclusion of foods identified as allergenic and allows the diet to be individualized [29].

Pharmacologic treatment

- Drug therapy is used in any patient in whom dietary treatment fails, or in whom allergy evaluation yields no evidence for a trial of diet-based therapy.
- Corticosteroid therapy is used most commonly in patient with idiopathic disease and usually produces excellent initial control of eosinophilia, vomiting, pain, and diarrhea. Corticosteroid-induced remissions are

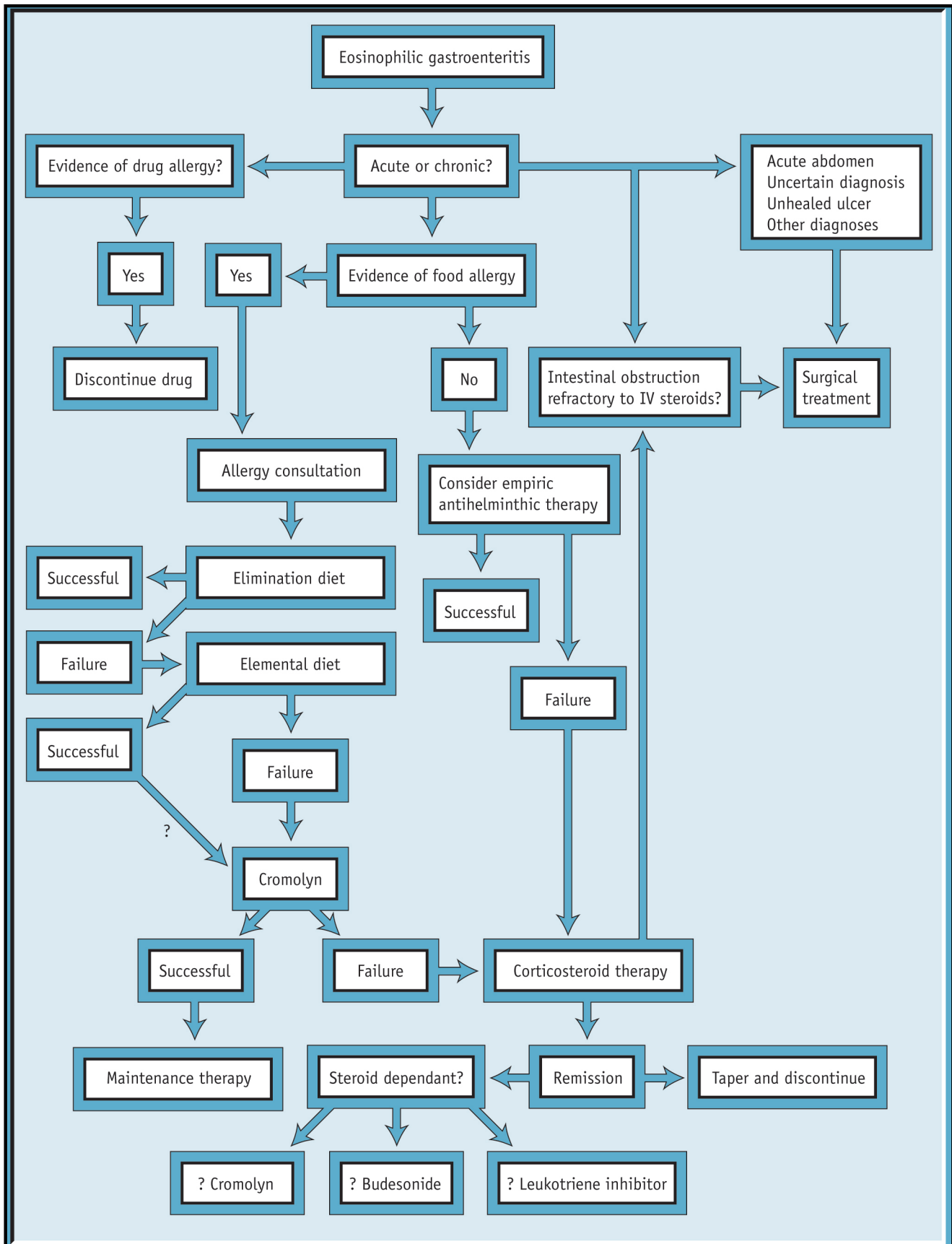


Figure 1. Algorithm for treatment of patients with eosinophilic gastroenteritis.

durable in about one half of patients after a few weeks of treatment. Other patients require maintenance treatment with nonsteroidal alternatives, alternate-day steroid dosing, or intermittent short courses of daily steroid therapy [3]. Steroid dependence should be prevented by assessment for allergy, search for agents to eliminate, and attempts at substitution of other agents if chronic drug treatment is indicated. Prednisone is described here as the most commonly used agent. Except for dosage, information for other steroids such as prednisolone and methylprednisolone is similar.

- Empiric antihelminthic therapy has been advocated by some authors [1,30].

Prednisone

Standard dosage	<i>Oral:</i> 20 to 40 mg/d for 1 to 2 weeks, followed by several weeks of dosage tapering. <i>Intravenous:</i> 40 to 60 mg/d. <i>Hydrocortisone:</i> 300 to 400 mg/d.
Contraindications	Uncontrolled diabetes, sepsis, fungal infections, administration of live vaccines.
Main drug interactions	Prednisone use enhances cyclosporine toxicity. Pharmacologic effect is diminished by barbiturates, hydantoins, rifampin. Systemic clearance is reduced by estrogen, ketoconazole, oral contraceptives.
Main side effects	Hypertension, increased intracranial pressure, headache, impaired wound healing, ecchymoses, purpura, striae, acne, cataracts, nausea, vomiting, dyspepsia, leukocytosis, salt and water retention, hypokalemia, muscle weakness, myopathy, osteoporosis, cushingoid state, growth suppression, hyperglycemia, masking of infection, insomnia.
Special points	Exclude infection with <i>Strongyloides</i> or treat empirically with antihelminthic prior to steroid administration.
Cost/cost-effectiveness	Inexpensive: 100 5-mg tablets of Deltasone (Pharmacia and Upjohn, Peapack, NJ), one of many brands available, cost \$4.53 wholesale [36].

Cromolyn sodium (disodium cromoglycate)

Standard dosage	The oral form (Gastrocrom [100 mg per 5 mL ampule]; Medeva Pharmaceuticals, Inc., Rochester, NY) is labeled for use in mastocytosis. Administer by diluting contents of the ampule in a glass of water as directed in patient instructions that accompany the product. The dosage may be reduced to minimum required to maintain symptom control after a therapeutic response is achieved. <i>Children younger than 2 years:</i> 20 mg/kg/d in four divided doses, which may be increased to 30/mg/kg/d. <i>Children aged 2 to 12 years:</i> 100 mg four times a day (at meals and at bedtime), not to exceed 40 mg/kg/d. <i>Adults:</i> 200 mg four times a day (at meals and at bedtime).
Contraindications	Hypersensitivity to cromolyn sodium.
Main drug interactions	None well documented.
Main side effects	Headache, diarrhea, bitter aftertaste, nausea, abdominal pain, glossitis, flatulence, pruritus.
Special points	The oral form is under investigation for symptoms of food allergy, eczema, urticaria pigmentosa, and hay fever. May allow withdrawal or reduction of steroid therapy. Anecdotal reports suggest it is most likely to be effective in patients with EGE due to food allergy.
Cost/cost-effectiveness	Comparatively expensive, but without the toxicity of steroids in long-term therapy. Ninety-six ampules (100 mg per 5 mL) cost \$181 wholesale. One day of therapy for an adult (eight ampules) costs \$15 wholesale [36].

Endoscopic therapy

- Endoscopic therapy is reserved for dilatation of esophageal strictures, as in reflux esophagitis and other causes of stricture.
- Dilatation may be combined with antireflux or steroid therapy as appropriate for the causative factors.

Endoscopic dilation

Standard procedure	Dilation may be done with balloon dilators through the endoscope or with oral dilators such as Maloney or Savary.
Contraindications	Same as for general upper endoscopy.
Complications	Multiple webs should be dilated cautiously, as mucosal laceration is common.
Cost/cost-effectiveness	Costs of endoscopy and materials.

Surgery

- Exploration for 1) diagnosis in acute abdomen or 2) in cases where endoscopy and imaging do not provide a diagnosis or empiric medical therapy fails.
- Relief of obstruction.

Exploratory and therapeutic surgery

Standard procedure	Intestinal resection, pyloroplasty, pyloromyotomy, or gastrectomy, depending on clinical presentation and organ involved.
Contraindications	Other major organ disease, chronic cardiopulmonary disease, advanced age, recent myocardial infarction.
Complications	Similar to standard operations for other indications. Depends on length and portion of bowel resected, if any.
Special points	May be delayed for a trial of parenteral steroids if there is a preoperative suspicion of EGE. Parasitism should be excluded preoperatively, and the pathologist should be aware of need for careful examination of tissues for parasitism.
Cost/cost-effectiveness	Expense of surgery and convalescence.

Emerging therapies

- Ketotifen has been reported effective in one EGE series, and is under investigation in patients with other digestive disorders and eosinophilic conditions. Ketotifen is not available in the United States, and there is insufficient evidence for recommendation of its use.
- There are single case reports of two leukotriene inhibitors. Montelukast, available in the United States, is labeled for chronic treatment and prophylaxis of asthma in adults and in children older than 2 years. It was reported as effective as therapy in one patient [37] and for maintaining remission in a steroid-dependent patient [38]. Suplatast tosilate, which is not available in United States, has been reported effective in a single patient [39]. There is insufficient evidence for recommendation.
- Previously available as a nasal spray and inhalant, the oral form of budesonide should be available in the United States at the time of publication of this article. It has been reported effective in maintaining remission in a single patient otherwise dependent on prednisone [40]. There is insufficient evidence for recommendation of its use.

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