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Eosinophilic Esophagitis Attributed to Gastroesophageal Reflux: Improvement With an Amino Acid–Based Formula

KEVIN J. KELLY,*,‡ AUDREY J. LAZENBY,§ PETER C. ROWE,* JOHN H. YARDLEY,‖ JAY A. PERMAN,*,‡ and HUGH A. SAMPSON*,¶

Divisions of ‡Pediatric Gastroenterology/Nutrition and ¶Pediatric Allergy/Immunology and Departments of *Pediatrics and ‖Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and §Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama

Background & Aims: **Treatment for gastroesophageal reflux may be ineffective in patients with an eosinophilic infiltration of the esophagus. The aim of this study was to investigate whether unremitting symptoms of gastroesophageal reflux and biopsy abnormalities of the esophagus may be associated with the ingestion of certain foods.** ***Methods:*** **Ten children previously diagnosed with gastroesophageal reflux by standard testing with long-standing symptoms (median, 34.3 months; range, 6–78 months) despite standard antireflux therapies, including Nissen fundoplication in 6 patients, were fed the elemental formulas Neocate or Neocate-1-Plus (Scientific Hospital Supplies Inc., Gaithersburg, MD) for a minimum of 6 weeks. Each child had repeat endoscopy followed by open food challenges.** ***Results:*** **While receiving the formulas, patients had either resolution (n = 8) or improvement (n = 2) of symptoms. On follow-up esophageal biopsy, the maximal intraepithelial eosinophil counts decreased significantly before (median, 41; range, 15–100) to after (median, 0.5; range, 0–22) the formula trial ($P = 0.005$). Other reactive epithelial changes of the esophageal mucosa also improved significantly. All patients redeveloped their previous symptoms on open food challenges.** ***Conclusions:*** **Chronic gastrointestinal symptoms and histological changes of the esophagus unresponsive to standard treatments for gastroesophageal reflux were improved by the use of elemental formulas. Symptoms recurred when specific dietary proteins were reintroduced during open food challenges. The mechanism of these observations is unknown.**

The presence of eosinophils in esophageal mucosal biopsy specimens is considered a highly specific marker for gastric acid reflux. In 1982, Winter et al. first correlated delayed clearance of acid from the esophagus measured by intraesophageal pH probe monitoring with an eosinophilic infiltration of the esophageal mucosa.[1] Esophageal eosinophils were also correlated with basal-zone hyperplasia and elongation of the vascular papillae, two findings considered representative of reactive changes of the esophageal epithelium to acid reflux.[2–4] Winter et al. concluded that the eosinophilic infiltration was also an early histological sign of acid reflux and that the more prominent the infiltration, the greater the duration or severity of the reflux. Since that report, an eosinophilic infiltration of the esophageal mucosa with or without basal-zone hyperplasia and elongated vascular papillae has been consistently interpreted as diagnostic of gastroesophageal reflux disease (GERD).[5–7]

We recently evaluated 10 pediatric patients with intractable symptoms attributed to GERD who also had long-term histological changes of the esophageal mucosa, including basal-zone hyperplasia, elongation of vascular papillae, and an eosinophilic infiltration. All 10 patients had the diagnosis of GERD made previously by one or more abnormal results of tests for reflux. Each patient had been compliant with several courses of standard antireflux medical therapies, although no treatment had resulted in the resolution of either the long-term symptoms or the esophageal mucosal abnormalities. Ultimately, 6 children had a Nissen fundoplication.

To explain these treatment failures, we proposed the following alternative hypothesis: the intractable symptoms and the esophageal eosinophilic infiltration were present not as a result of persistent acid reflux but rather as a result of a response to the ingestion of intact dietary proteins. We speculated that this response may be a hypersensitivity reaction. We further speculated that these patients may have regularly eaten these dietary proteins without an awareness of the relationship between the ingestion of the foods and the development of symptoms.

In previous studies, elimination of individual or multi-

Abbreviations used in this paper: GERD, gastroesophageal reflux disease.

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ple dietary proteins from an otherwise normal diet has failed to conclusively identify specific foods believed to be responsible for long-term symptoms attributed to gastrointestinal allergy. To test our hypothesis, we offered these patients a dietary trial designed to remove all intact, complex proteins as completely as possible from their diets for a defined period of time.

We report the prompt improvement of intractable symptoms previously attributed to GERD in these 10 patients, as well as the improvement of the long-term histological changes of the esophagus, after the substitution of nearly all common dietary protein antigens in the diet with an amino acid–based formula. Furthermore, symptoms of GERD were shown to recur after the controlled reintroduction of standard food challenges performed openly either at home or in the hospital. We speculated that these observed improvements in symptoms were caused by an unrecognized hypersensitivity state. Because we were unable, however, to collect pH probe data both before and after the institution of the elemental formula, this study cannot exclude the possibility that the elemental formula led to improvement by some direct or indirect effect on acid reflux.

Materials and Methods

Patient Identification

Seventy-five pediatric patients underwent repeat endoscopy with biopsy at The Johns Hopkins Children's Center between September 1992 and May 1994 for a second-opinion evaluation of their long-term reflux symptoms that had been unresponsive to standard medical therapies. Twenty-three of these patients showed persistence of the esophageal eosinophils similar to their initial biopsy specimens. The enrollment of patients for this study, as shown in Figure 1, was from this group of 23 patients. Seventeen of the 23 patients were offered the dietary trial; 6 of the 23 were treated by other physicians with different medications and were excluded from the study. Of the 17 patients offered the dietary trial, 12 patients complied. Five patients were not compliant with the restrictions of the trial and were excluded from our analysis. Of the 12 patients who completed the trial, 10 consented to undergo a follow-up endoscopy after the completion of the trial, and 2 patients refused to undergo the follow-up endoscopy even though their symptoms had resolved on formula.

In the 10 patients, 8 underwent all of their initial diagnostic testing for gastroesophageal reflux at their previous treatment facilities. The prior medical evaluations of these patients were reviewed and recorded, specifically the previous gastroenterology evaluation including any objective measurements for GERD and any previous allergy evaluations that included skin testing. Therefore, 8 of the patients included for analysis were children who had been referred to The Johns Hopkins Children's Center for a second opinion.

The prior treatments for reflux disease had been administered in these 8 patients at the previous care facilities. These medications included H_2-receptor antagonists (ranitidine or famotidine), liquid antacids, sucralfate, bethanecol, or metoclopramide. These medications had been prescribed in appropriate dosages in a variety of different combinations. The remaining 2 patients underwent their initial evaluations, biopsies, and treatment at The Johns Hopkins Children's Center.

Patients were identified for the trial during a routine outpatient interview if they reported persistence of their reflux symptoms despite compliance with their prescribed antireflux medications for 2 months or longer. The resultant 10 patients who completed the dietary trial and consented to undergo a follow-up endoscopy after the trial are the subjects of this report.

Reevaluation at The Johns Hopkins Children's Center

An initial upper endoscopy was performed in our hospital on the 10 compliant patients before the dietary trial. This procedure included collection of mucosal biopsy specimens from five sites: the second portion of the duodenum, the duodenal bulb, the gastric antrum, the gastric body, and the distal esophagus approximately 5 cm above the visualized z-line. All biopsy specimens were routinely fixed in formalin, embedded in paraffin, and stained with H&E.

Patients were excluded from this study if they had histological evidence of celiac disease, giardiasis, Crohn's disease, or *Helicobacter pylori*–associated gastritis or if they fulfilled the diagnostic criteria for eosinophilic gastroenteritis as described by Katz et al.[8] Specifically, patients were defined as having eosinophilic gastroenteritis if their biopsy specimens showed evidence of either a significant increase in the infiltration of eosinophils of the duodenum or if the gastric antrum showed either a marked eosinophilic infiltration or evidence of the epithelial necrosis and regeneration of the mucosa characteristic of eosinophilic gastroenteritis. No patient with eosinophilic gastroenteritis was included in this study.

If our patients' biopsy specimens showed persistent abnormalities in the esophageal mucosa consistent with GERD (including intraepithelial esophageal eosinophils, basal-zone hyperplasia, and elongation of vascular papillae), the patients were then offered the opportunity to participate in the dietary trial. All 10 patients included in the formula trial showed persistent histological evidence of gastroesophageal reflux, including eosinophilic esophagitis.

Dietary Trial

The dietary trial consisted of the substitution of a protein-free, l-crystalline amino acid–based formula (Neocate or Neocate-1-Plus; Scientific Hospital Supplies Inc., Gaithersburg, MD) for nearly all normal protein sources in the diet. These formulas are specifically designed to meet the nutritional requirements of infants younger than 1 year of age (Neocate), and children older than 1 year of age (Neocate-1-Plus). The formulas were prescribed in quantities sufficient to provide

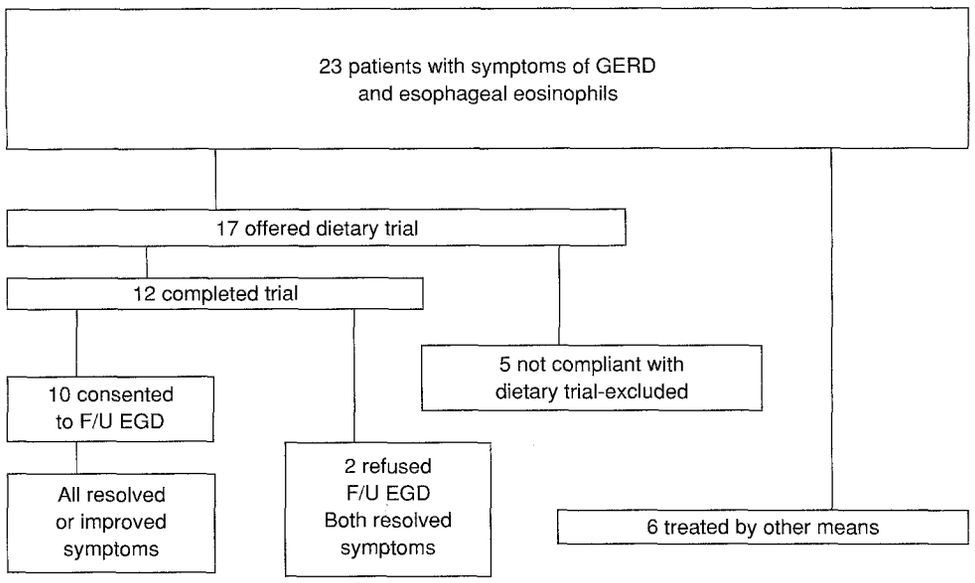


Figure 1. Enrollment of patients with long-term symptoms and persistent esophageal eosinophils previously attributed to GERD. EGD, esophagogastroduodenoscopy; F/U, follow-up.

adequate daily calories with the proper distribution of carbohydrates, fats, nitrogen, vitamins, minerals, and micronutrients for growth.

Informed consent was obtained before the start of the dietary trial. All formulas were provided free of charge to the families by the manufacturer throughout the course of the trial. The formula was recommended for a minimum of 6 weeks. Two patients took the formulas only by mouth, 4 took the majority of their formula orally with some enteral tube supplementation, and 4 patients took the formula exclusively by home-based nasogastric tube feedings. In addition to the formula, the patients were allowed ad libitum access to clear liquids. If the patients were old enough to eat solid foods, they were only permitted foods made from corn and apples. These two foods provided some oral-pharyngeal stimulation with their higher texture and some variety of taste. Corn and apples were chosen because hypersensitivity reactions to these two foods confirmed by double-blinded placebo-controlled food challenges have been extremely rare in other food allergic disorders. Therefore, the likelihood that either of these foods might be associated with the long-term symptoms was considered remote. No other solid foods or other sources of complex dietary proteins were permitted during the dietary trial.

The patients and their parents were asked to record any changes in the long-term gastrointestinal tract symptoms prospectively at home during the formula trial. The patients were evaluated in the clinic throughout the period of time on the formula. Weight gain, hydration state, and tolerance of the formula were monitored and recorded at regular intervals.

To change as few variables as possible from the symptomatic baseline, we chose to maintain all patients on their previous antireflux medications. No new medications were prescribed. Patients were excluded from the trial if they were receiving glucocorticoids or cromolyn sodium.

Postdietary Trial Evaluation

If symptomatic improvement occurred during the formula trial, upper endoscopy with biopsy was performed again. The biopsy specimens collected after symptomatic improvement were paired with the predietary trial biopsy specimens obtained at our facility. Every biopsy specimen was individually coded. Each coded biopsy specimen was then scored jointly by two gastrointestinal pathologists (J.H.Y. and A.J.L.) who were blinded to the patient's history, the previous pathologist's interpretations, the patient's therapeutic interventions, and symptomatic outcomes.

A scoring system was devised to grade the mucosal biopsy specimens. Each specimen from the duodenum, gastric antrum, gastric body, and esophagus was graded. The results were then tabulated, and the coded results were correlated for each patient. None of the resultant scores determined from the duodenal and gastric biopsy specimens showed statistically significant changes after the dietary trial. Only the esophageal data are presented in this report. The scoring system for the esophagus is shown in Table 1 and includes the evaluation of the following four histological findings of the squamous mucosa: active inflammation, the length of vascular papillae, basal-zone hyperplasia, and the number of intraepithelial eosinophils counted. Active inflammation was defined by the presence of neutrophils, erosions, or ulcers. An erosion was defined as the loss of the superficial mucosa accompanied by a fibrinoinflammatory exudate. Ulcerations were defined as loss of the entire thickness of the mucosa and were recognized as fragments of inflamed granulation tissue. On a low-power scan,

Table 1. Esophageal Inflammation Grading System

Active inflammation of epithelium
Grade 0, no neutrophils, exudates, erosions, or ulcerations
Grade 1, neutrophils present in <20% of epithelium but no erosions or ulcers
Grade 2, neutrophils present in >20% of the epithelium and/or erosions or ulcerations
Length of vascular pegs
Grade 1, $<^1/_3$ the distance from the base to the surface
Grade 2, $>^1/_3$ but $<^2/_3$ the distance from the base to the surface
Grade 3, $>^2/_3$ the distance from the base to the surface
Amount of basal-zone (immature) cells present
Grade 0, 1–2 cell layers thick
Grade 1, >2 cell layers thick but <20% the total thickness of the epithelium
Grade 2, >20% but <50% the total thickness of the epithelium
Grade 3, >50% the total thickness of the epithelium
Mucosal eosinophil count in area of maximal concentration (at 400×)

the best-oriented field of each specimen was identified jointly by the two pathologists. Vascular papillae elongation was determined by estimating the height of the vascular papillae relative to the total epithelial thickness. Basal-zone hyperplasia was determined by estimating the thickness of the immature cells of the basal zone relative to the thickness of the entire epithelium. A basal-zone cell was recognized by its bluish color and minimal cytoplasm. On a low-power scan, the heaviest area of eosinophils was determined, and the eosinophils were counted using a 40× objective lens (Olympus BH-2, DPlan 40× objective; Olympus, Lake Success, NY). A cell was counted as an eosinophil if it contained 1–2 rounded nuclear lobes and/or bright red, granular cytoplasm. Cells were not counted as eosinophils if they contained more than 2 lobes or had flattened nuclear lobes.

Predietary and postdietary biopsy specimen scores were compared using the nonparametric Wilcoxon signed rank test. A P value of <0.05 was considered significant. On repeat-blinded reading of the same slides ($n = 10$) at two different sessions separated by at least 1 month, the pathologists' combined assessment of the number of esophageal eosinophils counted per 40× field showed almost perfect correlation beyond chance (intraclass correlation coefficient, 0.96; $P < 0.005$).[9]

Open Food Challenges Performed at Home

After completion of the postdietary trial endoscopy, the parents were instructed to reintroduce foods to their children in an open, nonblinded fashion at home. The open, nonblinded format was chosen because no patient or parent had any prior suspicion of a relationship between foods and the long-term symptoms. To determine if the ingestion of any single dietary protein sources might reproduce any of the previous symptoms, the parents were instructed to introduce one source of protein at a time that had been previously eaten on a regular basis. Foods were introduced only when the child was free of any evidence of intercurrent or acute illnesses that might produce gastrointestinal tract symptoms. Each food was a single-sized serving prepared at home by the parent. The food was introduced twice daily for 3 consecutive days. Parents were instructed to record any symptoms observed or reported by the patient after the reintroduction of the food and the elapsed time from the reintroduction of each food until the recurrence of any observed or reported gastrointestinal symptoms. If a child had a history of a positive reaction to a food by prick-skin testing, the parents were instructed not to reintroduce that food at home.

Results

The median age of the study patients was 5 years (age range, 8 months to 12.5 years); 6 of the 10 study patients were boys (Table 2). Two of the 10 patients were mentally retarded with cerebral palsy and developmental delay; 1 of these 2 patients also had an Arnold–Chiari malformation with spina bifida, meningomyelocele, and neurogenic bladder. One child underwent surgical repair of a tracheoesophageal fistula with primary anastomosis of the esophagus during infancy and also underwent repair of an imperforate anus. Five children had been diagnosed with asthma and 2 with eczema.

Symptoms

The reported symptoms as outlined in Table 2 were all consistent with the diagnosis of GERD in children.[10] A reported characteristic of the recurrent emesis was peculiar. The vomitus contained a thick, gelatinous mucous described by the parents as similar in appearance to "uncooked egg whites." This mucoid emesis was reported in all 10 patients at some point in their history. The 10 patients had been symptomatic for a median of 27 months (range, 6–78 months). The antireflux medications administered previously are listed in Table 2. The median number of medications for each patient was two (range, 1–4). The 6 patients who had undergone the Nissen fundoplication reported improvement of their emesis postoperatively, but their abdominal pain persisted, especially in the postprandial period. As a result, their oral intake was poor. Three of these 6 patients depended on gastrostomy tube feedings for growth. However, each patient reported the occurrence of abdominal pain whenever they were fed standard proprietary formulas via their gastrostomy tube.

Previous Studies for GERD

Each patient had prior, objective evidence of GERD. Seven patients had abnormal reflux documented by intraesophageal pH probe studies, 7 had reflux on

Table 2. Study Patient Characteristics

Patient	Sex	Age	Long-term presenting symptoms	Duration of symptoms (*mo*)	Objective evidence of reflux	Prior medical/surgical treatments	Time for improvement on formula (*wk*)
1	M	8 mo	Poor weight gain, mucous emesis	6	RMS, UGI, pH probe, esophagitis[a]	Ranitidine	3
2	M	30 mo	PDIE, food refusal, poor weight gain, mucous emesis, diarrhea	12	UGI, esophagitis	Metoclopramide	4
3	M	32 mo	PDIE, food refusal, poor weight gain, mucous emesis	27	UGI, esophagitis	Famotidine Tagamet	2
4	F	33 mo	PDIE, food refusal, poor weight gain, mucous emesis	14	Esophagitis	Ranitidine, metoclopramide	3
5	F	3.5 yr	PDIE, food refusal, abdominal pain	23	RMS, pH probe, UGI, esophagitis	Nissen, ranitidine, metoclopramide	2
6	M	4 yr	PDIE, food refusal, abdominal pain	40	RMS, pH probe, UGI, esophagitis	Nissen, ranitidine, metoclopramide	4
7	M	5 yr	PDIE, food refusal, abdominal pain	35	UGI, pH probe, esophagitis	Nissen, ranitidine, Carafate	3
8	M	5 yr	PDIE, poor weight gain, abdominal pain	48	UGI, pH probe, esophagitis	Nissen, ranitidine, metoclopramide	4
9	F	9.5 yr	PDIE, abdominal pain	60	Esophagitis, pH probe	Nissen, ranitidine, metoclopramide, Carafate, bethanechol	6
10	F	12.5 yr	PDIE, food refusal, abdominal pain	78	Esophagitis, pH probe	Nissen, ranitidine, famotidine	6

[a]Esophagitis was diagnosed according to the results of a biopsy.
PDIE, profound disinterest in eating; pH probe, 24-hour intraesophageal pH study; RMS, radionuclide milk scan; UGI, barium upper gastrointestinal series.

barium upper gastrointestinal studies, 1 had an abnormal radiolabeled milk scan, and all 10 had esophagitis when they underwent upper endoscopic biopsy (Table 2). The seven abnormal pH probe scores were determined at the previous facilities by a variety of different scoring techniques. None of these tracings was available to us for review. We repeated a 24-hour pH probe study on 1 patient at the request of the parents. The child had undergone a Nissen fundoplication but showed persistent histological evidence of eosinophilic esophagitis. This study failed to show any acid reflux above the intact fundoplication.

Skin Testing and Allergy History

Three patients were diagnosed previously with food allergies confirmed by prick-skin testing; 2 of these 3 patients had a past history of anaphylaxis with the ingestion of certain foods. These patients had been previously under the care of an allergist, but despite rigid restriction of the foods to which they were skin-test positive, their chronic gastrointestinal symptoms persisted. Because these 3 patients had removed all skin-test–positive foods that had caused immediate skin-test reactions from their diets, their long-term reflux symptoms had not been considered associated with the intake of food. The remaining 7 patients had no history of food allergies and had not previously undergone skin testing. Therefore, there was no clinical suspicion of hypersensitivity to foods in any of these 7 patients. Six of these 7 patients were skin tested before the dietary trial to a minimum of six foods. In 3 patients, all foods tested were negative, and 3 patients were positive to four or fewer foods. Of the 2 patients with an available absolute eosinophil count before the trial, both were within the normal range for our laboratory at 366 and 393/mm^3 (normal range, 150–440/mm^3).

Predietary Trial Endoscopic Findings

In 8 patients, the gross appearance of the esophageal mucosa on the predietary trial endoscopy supported the clinical suspicion of persistent GERD. Visual changes of erythema suggestive of injury from acid reflux were present in these 8 patients, 1 of whom also appeared edematous. The child who had undergone repair of the trached esophageal fistula had narrowing and ulceration with stricture.

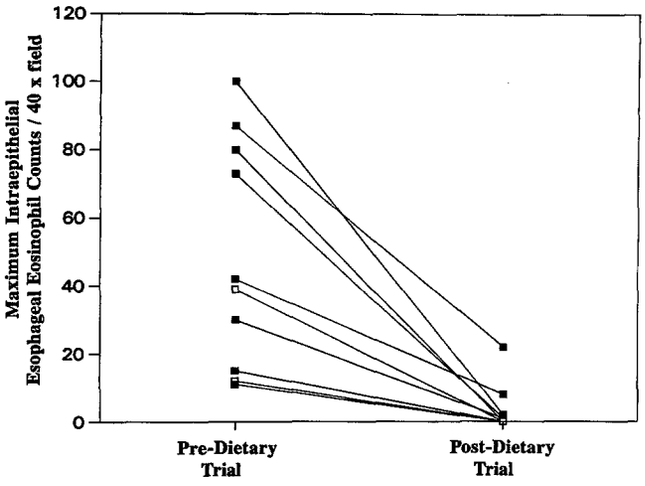


Figure 2. Maximal intraepithelial esophageal eosinophil counts predietary and postdietary trial with an amino acid–based formula. ■, The 8 patients who reported complete resolution of symptoms; □, the 2 patients who reported improvement. The difference between the predietary and postdietary trial maximal intraepithelial eosinophil counts was significant ($P = 0.005$, Wilcoxon signed rank test).

Outcome of the Dietary Trial

The patients remained on the dietary trial for a median of 17 weeks (range, 6–58 weeks). During the dietary trial, 8 of 10 patients became free of their long-term complaints, and 2 patients reported substantial improvement but not complete resolution of their symptoms. The median time for improvement of symptoms while on the elemental formulas was 3 weeks (range, 2–6 weeks) (Table 2).

There were no untoward effects or adverse reactions to either of the formulas in any of the patients during their dietary trials. All patients maintained adequate hydration, and while on the formula, each patient showed appropriate advancement of height and weight.

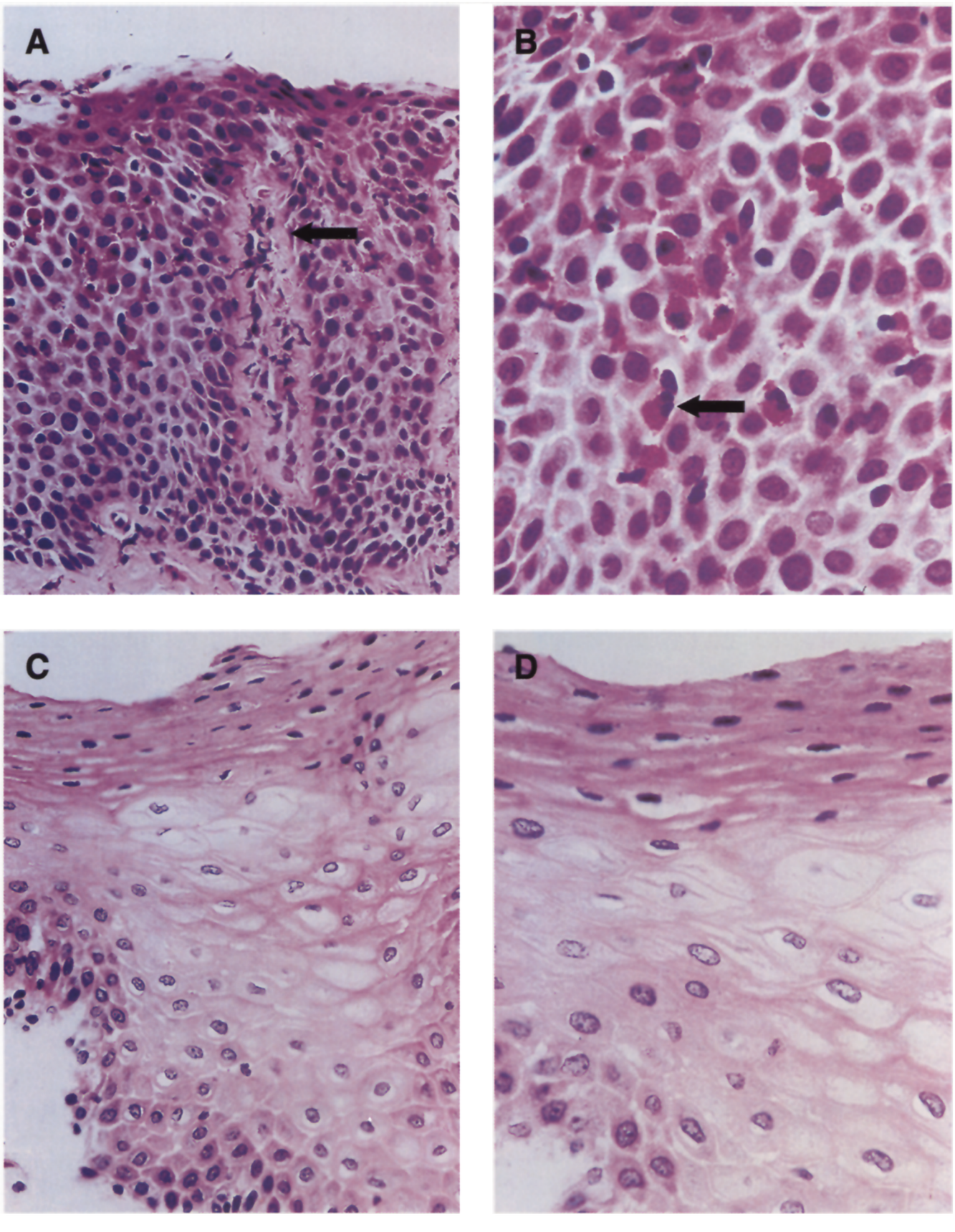
Postdietary Trial Endoscopy and Histopathologic Results

After the dietary trial, 6 patients showed resolution of their gross, pretrial esophageal abnormalities on upper endoscopy. Two patients had persistence of the mild erythema of the esophagus, including the patient with the trached esophageal fistula repair. Comparison of the paired esophageal biopsy specimens showed a significant reduction in the degree of the eosinophilic infiltration of the mucosa in all 10 patients, including complete resolution of the eosinophils in 5 patients. As shown in Figure 2, the maximal esophageal intraepithelial eosinophil count per 40× field decreased from a median of 41 (range, 15–100) before the formula trial to 0.5 (range, 0–22) in the postdietary trial biopsy specimen ($P = 0.005$, Wilcoxon signed rank test). The median grade for basal-zone hyperplasia decreased from 3 before the dietary trial to 1 in the postdietary trial biopsy specimen ($P = 0.005$, Wilcoxon signed rank test). Only 7 of the 10 patients had paired biopsy specimens with adequate orientation to accurately determine the lengths of vascular papillae. The predietary trial biopsy specimen of these 7 patients was scored as grade 3. In 4 patients, the elongation of vascular papillae improved from grade 3 to 1, whereas 3 patients showed no change in this finding ($P = 0.043$, Wilcoxon signed rank test). No findings of acute inflammation were noted in either the predietary or postdietary trial biopsy specimens. Figure 3 shows a comparison of photomicrographs of the esophageal mucosal biopsy specimens of 1 of these patients before and after the dietary trial.

Results of the Open Food Challenges

Open challenge with specific foods recreated symptoms identical to those experienced before the dietary trial in 9 of 10 patients. The specific food protein sources identified on open challenge included cow milk in 7 patients, soy protein in 4 patients, wheat in 2 patients, peanut in 2 patients, and egg in 1 patient. Patients showed symptomatic responses to a median of two foods for each patient (range, 1–6 foods). Symptoms developed a median of 1 hour (range, 0.5–8 hours) after the controlled reintroduction of the foods. The challenges reproduced the peculiar mucous-containing emesis as well as gagging, retching, irritability, abdominal pain, and anorexia. One patient also developed an urticarial rash. The 1 patient in whom a specific food could not be identified had a past history of significant responses to a number of skin-test–positive foods. This patient was not challenged with any of these foods.

Figure 3. (*A*) An esophageal biopsy specimen from a patient while symptomatic on an unrestricted diet shows elongated vascular papillae (*arrow*), a greatly expanded zone of immature cells (basal-zone hyperplasia), and numerous eosinophils. (*B*) A higher-power image of the same biopsy specimen highlights the eosinophils (*arrow*) and the immaturity of the squamous cells with minimal cytoplasm and enlarged nuclei. (*C*) An esophageal biopsy specimen taken from the same patient who resolved her long-term symptoms after completion of the 8-week amino acid–based formula trial shows normal squamous epithelium with only 1–2 layers of immature cells at the base of the mucosa with short vascular papillae and no eosinophils. (*D*) A higher power of the same biopsy specimen shown in *C* highlights the maturity of the squamous cells with abundant pink eosinophilic cytoplasm and progressively smaller nuclei (H&E; original magnification: *A* and *C*, 400×; *B* and *D*, 630×).


A
B
C
D

Once the offending food was identified and eliminated, these patients were free of symptoms or have remained with improved symptoms for up to 6 months. All patients have been able to discontinue the formula, and 7 of the 8 patients who had required tube feedings no longer use the enteral tube. Except for their dietary restrictions, these patients have been maintained on an otherwise regular diet. Eight of the 10 patients have discontinued their previous antireflux medications. Review of the previous skin-test results showed that none of the identified foods that produced a positive challenge had produced a positive skin-test result. It is likely that challenge with a skin-test–positive food would have produced symptoms, but this challenge was not undertaken in this study.

Discussion

This study has shown that 10 pediatric patients who were placed on a highly restricted diet and supplemented with an amino acid–based formula experienced a prompt, sustained improvement in long-term gastrointestinal symptoms that had been attributed previously to GERD. These 10 patients had objective evidence of reflux that had been unresponsive to standard antireflux therapies, including a Nissen fundoplication in 6 patients. The improvement in symptoms occurred within 3 weeks of the start of the dietary trial and was striking to the parents and patients, some of whom had been symptomatic for as long as 6 years. These observations suggest that a variety of common gastrointestinal symptoms, such as long-term abdominal pain, poor appetite, early satiety, a profound disinterest in eating, poor weight gain, and vomiting of an unusual thick, gelatinous mucus, can be related to the ingestion of common dietary proteins in certain susceptible children.

Sequential endoscopy performed at the end of the dietary trial showed improvement in the gross and histological abnormalities of the esophagus that had been attributed previously to chronic GERD. Significant improvements were noted in the number of intraepithelial esophageal eosinophils in the hyperplasia of the basal zone and in the elongation of the vascular papillae.

Once improvement of the long-term symptoms and esophageal histology occurred, open food challenges performed at home by the parents of these patients identified specific foods that caused recurrence of the previous gastrointestinal symptoms in 9 of 10 patients. In these 9 patients, common foods such as milk, egg, and soy were associated with the recurrence of symptoms. The ability to reliably identify which dietary protein antigens might be responsible for symptoms in patients with an eosinophilic infiltration of the gastrointestinal tract has always been difficult. In past reports, most of the dietary manipulations, such as rigid restriction or sequential elimination, have proven unreliable and have been a source of frustration to both patients and clinicians.[11,12] Most of these reports have involved patients with the diagnosis of eosinophilic gastroenteritis.[13] None of the reports of these unsuccessful trials have defined how the dietary components were selected for removal, how the completeness of the restriction was assured, or how the nutritional adequacy of the resultant diet was maintained.

For our trial, the relationship between the ingestion of food and the development of symptoms became evident only after all dietary proteins were removed and substituted with an amino acid–based formula for a sustained period. These formulas permitted us to remove all sources of exogenous dietary protein from these patients as completely as possible, while at the same time providing an adequate source of nitrogen for growth. The difficulties encountered in past studies associated with attempts to identify the specific, individual, and causative proteins in the diet by other means thus were obviated. In 3 of our patients who had undergone elimination of skin-test–positive foods, symptomatic improvement did not occur. These observations are in agreement with other reports that skin testing for immediate hypersensitivity responses is an unreliable means of identification of foods associated with the development of gastrointestinal tract symptoms.[12,14]

Once a symptom-free baseline was achieved, the controlled reintroduction of individual dietary proteins provided the opportunity to record the temporal relationship between the ingestion of the test protein and the development of symptoms. Our data showed a delay of several hours (to a maximum of 8 hours) between the food challenge and the symptomatic response. We believe that this time lag may explain, in part, why none of these patients, their parents, or their prior care providers had any suspicion of the relationship between the ingestion of the identified foods and the occurrence of the long-term symptoms.

Our data showing the temporal relationship between the ingestion of specific dietary protein and the redevelopment of upper gastrointestinal tract symptoms were derived from reports of open, uncontrolled challenges performed by the parents. Because both open and single-blinded challenges fail to control for psychogenic factors as well as patient, parent, and physician bias, our observations must be verified on double-blinded, placebo-controlled food challenges. The double-blinded, placebo-controlled food challenge is the current gold standard

for the confirmation of food-related responses.[15] Studies are currently underway to determine if our observations can be confirmed by double-blinded, placebo-controlled food challenges.

The improvement of the esophageal mucosal biopsy specimens after a period of time on the amino acid–based formulas suggests that the previous histological abnormalities may have been related to the intake of intact dietary proteins. The suspected injurious effect of an intact source of protein on the esophageal mucosa may be analogous to the effect of gluten on the duodenal mucosa in celiac disease. However, we have not yet shown the recurrence of abnormalities of the esophageal mucosa after the reintroduction of the identified offending foods.

Our hypothesis suggested an immunologic basis for the long-term symptoms. Although several of our patients had atopic histories, our data did not support an immunoglobulin E–mediated mechanism for the gastrointestinal symptoms. However, the reproducibility of the responses with each protein exposure, as well as the temporal relationship between the protein exposure and the symptomatic response, suggest the possibility of a delayed-type hypersensitivity response. Further studies are underway in our facility to investigate the possibility of a cell-mediated hypersensitivity response involving esophageal mucosal lymphocytes and circulating peripheral lymphocytes.

It is possible that the observations in these 10 patients do not involve immunologic mechanisms. The amino acid formulas may exert some other nonimmunologic influence on gastrointestinal tract function that may account for our symptomatic and histological improvements. For example, the amino acid–based formulas may alter upper gastrointestinal tract motility or reduce basal acid output, or these formulas may act to influence lower esophageal sphincter function to reduce the frequency or severity of reflux. Finally, the liquid diet itself may decrease the frequency or severity of acid reflux, but 3 of the patients presented were maintained exclusively on liquid-formula diets containing whole, cow-milk protein before changing to the amino acid–based formula. For these 3 patients, the motility pattern would most likely be similar, although no formal motility studies were performed. The specific physiological responses to the ingestion of the amino acid–based formulas and the mechanisms of these responses remain to be determined. The possibility that the elemental formula caused these observed improvements by either a direct or indirect effect on acid reflux is unknown. Further studies will be required to determine whether the improvement while taking elemental formula is caused by its effect on acid reflux or on a hypersensitivity state.

Prior reports involving eosinophilic esophagitis exist in the literature but are relatively rare. In the past, eosinophilic esophagitis has been associated with a variety of different disease states. The finding has been associated with atopic disease in a patient with an eosinophilic infiltration elsewhere in the gastrointestinal tract.[16] Achalasia requiring surgical treatment was associated with an esophageal eosinophilia in a patient reported also to have a persistent, peripheral eosinophilia.[17] This association between an esophageal eosinophilia and an elevated peripheral eosinophil count has been found by other investigators.[18] Lee[19] studied 11 patients with marked esophageal eosinophilia. Lee concluded that 10 of 11 patients had severe reflux esophagitis based on barium swallow, pH probe, or endoscopic findings. However, Lee had follow-up data on only 1 of these 10 patients who did have clinical and histological improvement on antireflux therapy. Lee concluded that the remaining patient with marked esophageal eosinophilia had "idiopathic eosinophilic esophagitis" based on the absence of documented reflux, a peripheral eosinophilia, small bowel involvement, and response to steroids. This report also further strengthened the association between an eosinophilic esophagitis and an allergic predisposition. Symptomatic improvement of a patient with an esophageal eosinophilia after treatment with systemic corticosteroids has also been reported.[20] However, none of our patients showed eosinophilic infiltrations in the other locations of the upper gastrointestinal tract.

To our knowledge, only one other report has described a group of patients with upper gastrointestinal tract symptoms and an eosinophilic infiltration of the esophagus without an eosinophilic infiltration of the stomach or duodenum.[21] In this report of 12 adult patients, each with more than 20 eosinophils per high-power field in the esophageal mucosa, 5 patients did not show evidence of GERD. Only 2 of these patients showed evidence of eosinophils in other organs of the alimentary tract, although only 6 of the patients had biopsy specimens taken from other sites. Only 1 of these patients had an elevated peripheral eosinophil count. Seven of these patients had some evidence of allergic disease, but none was evaluated for the possibility of food allergy. These adult patients differed from our patients in that the dominant presenting symptom was dysphagia. However, there was overlap between the histological findings of our patients with long-term symptoms attributed to reflux esophagitis and the idiopathic eosinophilic esophagitis without reflux described in this study.[21]

In all previous studies dealing with eosinophilic esophagitis, regardless of the symptomatic presentations, none

has considered the possible relationships between reported symptoms, the inflammatory response, and the intake of food. Our data, which relate long-term symptoms to the ingestion of specific foods, are derived from a series of patients with intractable symptoms attributed to GERD recorded over a long period of time. Our observations suggest that there is a relationship between the intake of common food proteins and these symptoms. A dietary trial that incorporated an amino acid–based formula, Neocate or Neocate-1-plus for our patients, in conjunction with a highly restricted diet for a defined period of time helped us determine the correct course of therapy.

In summary, the differential diagnosis of pediatric patients with common gastrointestinal symptoms characteristic of GERD who have an eosinophilic infiltration of the esophageal mucosa should include a consideration of hypersensitivity to dietary proteins in addition to a consideration of GERD, regardless of the results of prick skin testing to foods. If a diagnosis of GERD in children is based on the presence of abnormal objective parameters of reflux, such as pH probe studies, barium contrast studies, and esophagitis with intraepithelial eosinophils, and if these patients fail to improve with standard treatment, then the consideration of a food-related hypersensitivity response should be considered. A possible food-related response should be investigated before the decision to perform a surgical antireflux procedure. The use of an amino acid–based formula as a supplement to a rigidly applied restrictive diet seems to facilitate the identification of foods responsible for the symptomatic and inflammatory responses in some of these patients. These observations warrant confirmation and further study.

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Address requests for reprints to: Kevin J. Kelly, M.D., Division of Pediatric Gastroenterology, Brady 320, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21287. Fax: (410) 955-1464.

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