

Prevalence and Outcome of Allergic Colitis in Healthy Infants with Rectal Bleeding: A Prospective Cohort Study

*Stavra A. Xanthakos, §Jeffrey B. Schwimmer, ||Hector Melin-Aldana, ‡Marc E. Rothenberg, †David P. Witte, and *Mitchell B. Cohen

*Division of Gastroenterology, Hepatology, and Nutrition, †Division of Pathology and Laboratory Medicine, ‡Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio; §Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego, San Diego, California; ||Division of Pathology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

ABSTRACT

Objectives: Allergic colitis is often diagnosed clinically in healthy infants with rectal bleeding and often treated with costly hypoallergenic formula. The true prevalence of allergic colitis is unknown. We tested the hypothesis that allergic colitis is overdiagnosed in healthy infants with rectal bleeding. The authors also determined whether rectal bleeding in infants without allergic colitis would resolve without diet change.

Methods: For the purposes of this study, allergic colitis was defined histologically as colonic mucosa with ≥ 6 eosinophils per high power field and/or eosinophils in colonic crypts or muscularis mucosae. We surveyed all 56 Ohio NASPGHAN members to determine standard practice regarding the evaluation of rectal bleeding in infants. In addition, infants ≤ 6 months old with rectal bleeding were recruited from the referral area of Cincinnati Children's Hospital Medical Center. All infants underwent flexible sigmoidoscopy with biopsies at 5, 10 and 15 cm. Formula or maternal diet was changed only for infants with histologic findings of allergic colitis as defined.

Study subjects were followed for 9 weeks.

Results: In the survey of NASPGHAN members, 84% indicated they would empirically change the diet of an infant with rectal bleeding to treat presumed allergic colitis. In our study population, however, only 14 of 22 (64%; 95% confidence interval, 41–83) infants with rectal bleeding had allergic colitis. Five (23%) had normal biopsies and three (14%) had non-specific colitis. Rectal bleeding in all infants with normal biopsies or nonspecific colitis resolved without diet change except for 1 infant subsequently diagnosed with infantile inflammatory bowel disease.

Conclusion: A significant proportion of infants with rectal bleeding may not have allergic colitis and may undergo unnecessary, expensive formula or maternal diet changes that may discourage breast-feeding. *JPGN* 41:16–22, 2005. **Key words:** Allergic colitis—Eosinophilia—Rectal bleeding—Cow's milk protein hypersensitivity—Flexible sigmoidoscopy. © 2005 Lippincott Williams & Wilkins

INTRODUCTION

Rectal bleeding is a common problem in infancy (1). The differential diagnosis of rectal bleeding in infancy includes common conditions such as allergic colitis (AC), anal fissures, infectious colitis and lymphoid

nodular hyperplasia and less common conditions such as necrotizing enterocolitis, Hirschsprung enterocolitis and inflammatory bowel disease (2–4). The prevalence and natural history of AC in infants are unknown. Signs of AC are nonspecific but typically include bloody diarrhea with mucus. Unfortunately no noninvasive test is diagnostic of AC, and the diagnosis is often made presumptively in healthy infants in whom anal fissures and infectious colitis have been excluded. This in turn leads to empiric therapy with hypoallergenic formula or elimination of all cow's milk proteins from the diet of breast-feeding mothers.

Current therapy for infants with AC is the elimination of presumed triggering antigens (5). The diet of formula-fed infants is typically changed to a protein hydrolysate formula (PHF). For infants who are breast-fed, cow's milk protein is generally eliminated from the maternal diet or breast-feeding is discontinued and PHF is initiated.

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Address correspondence and reprint requests to Mitchell B. Cohen, Division of Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, MLC 2010, 3333 Burnet Avenue, Cincinnati, OH 45229-3039. (e-mail: mitchell.cohen@cchmc.org).

PHF is more expensive than standard infant formula. In some infants bleeding does not resolve with this change and the diet is changed to an elemental L-amino acid (LAA) formula that is even more expensive.

The aim of this prospective study was to determine the prevalence of AC in a population-based cohort of healthy infants with rectal bleeding. We tested the primary hypothesis that less than 70% of infants 6 months old with rectal bleeding would have biopsy-proven AC. We felt that this percentage of "misdiagnosis" was clinically significant and allowed us to have a practical sample size. Secondly, we hypothesized that bleeding in infants without AC would resolve without dietary change.

MATERIALS AND METHODS

Subjects

The study and consent forms were approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. The parent of each subject provided informed consent before enrollment. Twenty-two infants with rectal bleeding were recruited from the Greater Cincinnati Metropolitan area (Pediatric Gastroenterology Clinic, Cincinnati Children's Hospital Medical Center Emergency Department and directly from community pediatricians who had been informed of the study). Inclusion criteria were age less than 6 months, no prior exposure to PHF or LAA formulas, no evidence of bleeding diathesis by history or physical examination and negative stool cultures. Rectal bleeding was confirmed at entry by

hemocult testing. All subjects were evaluated by history and physical examination for signs of infection, Hirschsprung disease, inflammatory bowel disease, coagulation disorders and allergic disease. A complete blood count with differential was performed to screen for anemia, thrombocytopenia and eosinophilia. Immunoglobulin (Ig)E concentration in serum was also obtained as a marker of allergic activation. Two initially enrolled subjects whose parents then refused to permit flexible sigmoidoscopy were not included in the final cohort of 22 patients (Fig. 1).

Pathology

A limited (15-cm) flexible sigmoidoscopy with pinch biopsies was performed in the office procedure room with the assistance of a trained endoscopy nurse. The procedure was done without sedation or preparation of the colon (clean out). Biopsies were taken at 5, 10 and 15 cm from the anus, targeted to areas with gross endoscopic findings, if present. One biopsy at each site was fixed in 10% formalin and processed for paraffin embedding, sectioning and standard hematoxylin and eosin staining. The biopsy was examined for routine histology by 1 of 2 pathologists participating in the study. The pathologists were not blinded to the patient history.

Although there are no standard accepted criteria for the diagnosis of infantile AC, several studies have demonstrated consistent but nonspecific histologic findings (4,6–8). Eosinophilic infiltration throughout the mucosal layers, particularly in the lamina propria, is characteristic. Winter et al. reported that greater than 60 eosinophils per 10 high-power fields in the lamina propria is strongly suggestive of AC (8). Eosinophils in

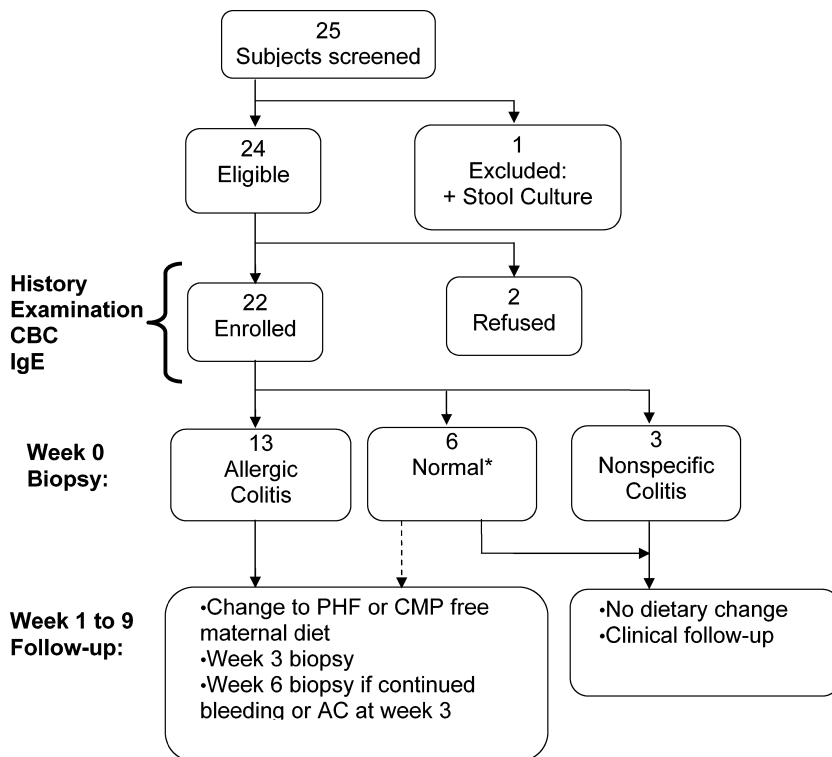


FIG. 1. Study flowchart. *One of the infants with normal histology was biopsied again at week 3 because of worsening bleeding and was found to have allergic colitis. This infant was then treated per protocol with the other 13 infants with allergic colitis.

crypts or interspersed in the muscularis mucosae are also highly associated with AC (9,10). The mucosal architecture is usually intact (9). The histologic criteria we used in this study for the diagnosis of AC was 6 or more eosinophils per high power field in the lamina propria (average of 60 eosinophils per 10 high power fields) or any eosinophils in the crypt epithelium or muscularis mucosae. These relatively liberal criteria would if anything favor the overdiagnosis of AC and thus would not provide a bias in favor of our hypothesis.

Nonspecific colitis was defined as a significant increase in the number of inflammatory cells in the lamina propria and/or neutrophilic cryptitis, without eosinophilia, significant glandular architectural distortion, microorganisms, granulomas or basal plasmacytosis.

Treatment and Follow-up

All subjects were followed for 9 weeks to assess outcome. Subjects were treated according to the diagnosis established by histopathology. Patients who did not meet the criteria for AC and did not have another treatable etiology for rectal bleeding did not have any feeding changes made but were followed clinically for resolution of gross bleeding. Assessment of rectal bleeding during the follow-up period was qualitative and assessed by parental self-report.

Subjects with a histologically confirmed diagnosis of AC were divided into formula-fed and breast-fed groups. The infants receiving cow's milk or soy formula were switched to a PHF (Alimentum®, Ross Products Division, Abbott Laboratories, Inc., Columbus, OH). Parents were instructed to observe stools for gross evidence of bleeding. At 3 weeks all subjects underwent a repeat sigmoidoscopy with biopsy. Three weeks was chosen to allow enough time for healing and minimize the dropout rate. Patients with no bleeding at week 3 and normal histology continued with PHF and were followed clinically for resolution of bleeding without repeat biopsy. Subjects whose bleeding resolved but who had persistent evidence histologically of AC were asked to continue using PHF and undergo a repeat biopsy after week 6 to assess for histologic improvement. If a subject continued to have gross bleeding and histologic evidence of AC at week 3, the diet was changed to an LAA formula (Elecare®, Ross Products Division, Abbott Laboratories, Inc., Columbus, OH) and a follow-up biopsy was also done at week 6.

Breast-feeding mothers of infants with AC were encouraged to continue breast-feeding but were asked to eliminate cow's milk protein from the diet and were given specific instructions. As with formula-fed infants, those with cessation of bleeding and normal biopsies had no further dietary changes or biopsies after week 3. Those with cessation of bleeding but continued histologic evidence of AC at the week 3 biopsy had no dietary change but were asked to have a repeat biopsy at week 6. Those who had both persistent bleeding and histologic evidence of AC at week 3 were changed to a PHF and underwent repeat biopsy at week 6. At week 6, if there was continued gross bleeding and persistent histologic AC, the diet was changed to an LAA formula. After 9 weeks, all subjects were offered clinical follow-up.

Survey

A separate survey tool was used to poll all 56 members of the North American Society for Pediatric Gastroenterology,

Hepatology and Nutrition (NASPGHAN) in the state of Ohio to determine clinical practice among pediatric gastroenterologists in diagnosis and treatment of infant AC. The 3-question survey was designed to assess initial response to an infant younger than 6 months with asymptomatic rectal bleeding and the approach to the same infant 3 weeks after initiating therapy (Table 1). We also wished to determine if our histologic definition of AC was considered acceptable by practicing pediatric gastroenterologists. If empirical therapy was chosen, participants were asked what type of dietary change they would recommend for formula-fed or breast-fed infants.

Statistics

For the null hypothesis, we estimated that the prevalence of allergic colitis among healthy infants with rectal bleeding would be 70%. With a sample size of 36, the 2-sided 95% confidence interval for a single proportion using the large sample normal approximation would extend 0.15 from the expected proportion of 0.70. However, because of difficulty in recruiting infants as a result of prior treatment by referring physicians with hypoallergenic formula, enrollment was terminated after screening 25 infants. For our primary outcome, the prevalence of AC among infants was determined and the 95% confidence interval was calculated.

Serum IgE and eosinophil counts were compared between the allergic colitis group ($n = 14$) and normal biopsy group ($n = 5$). The nonspecific colitis group was excluded from comparison because of its small size ($n = 3$). The serum IgE levels were not normally distributed so a natural-log transformation was done. The means of the natural-log serum IgE and eosinophil count were compared using the 2-sample Student *t*-test. All analysis was run using the statistical software package SAS, version 8.2 (SAS Institute, Inc., Cary, NC).

TABLE 1. Survey questions

1. In otherwise healthy infant less than 6 months old with asymptomatic rectal bleeding and a normal physical examination, would you:
 - A. Empirically change to a protein hydrolysate formula (PHF) and/or instruct a breast-feeding mother to eliminate all milk protein from her diet.
 - B. Empirically change to an L-amino acid formula and/or instruct a breast-feeding mother to eliminate all milk protein from her diet.
 - C. Obtain sigmoidoscopic biopsies to confirm the diagnosis before changing the formula or maternal diet.
 - D. Other: (write in)
2. If the infant described above continues to have asymptomatic rectal bleeding 3 weeks after a dietary change to a PHF or maternal cow's milk protein free diet, would you:
 - A. If formula feeding, change from a PHF to an L-amino acid formula or if breast-feeding, stop breast-feeding and change to a PHF.
 - B. Obtain biopsies to confirm diagnosis before further changes in dietary therapy.
 - C. Other: (write in)
3. What are your histologic criteria for allergic colitis?
 - A. Acute eosinophilic inflammation with greater than 6 eosinophils per high power field and/or eosinophils in the crypt epithelium or muscularis mucosae.
 - B. Other: (write in)

PHF, protein hydrolysate formula.

RESULTS

Prevalence of Allergic Colitis

Twenty-two subjects were enrolled and underwent flexible sigmoidoscopy at onset of study (Fig. 1). One infant had normal histology at enrollment despite endoscopic erythema, ulceration, friability and lymphoid nodular hyperplasia (LNH). This infant underwent repeat biopsy at week 3 because of worsening bleeding and was subsequently found to have AC. Therefore, the overall prevalence of AC in our study was 14 of 22 or 63.6% (95% confidence interval, 40.7–82.8). Five of 22 infants (22.7%) had normal biopsies, and 3 had non-specific colitis (13.6%). Subject characteristics are summarized in Table 2 and the symptoms at presentation are listed in Table 3. There were no distinguishing characteristics or symptoms that differentiated the AC infants from the other groups.

Endoscopic Findings

Gross endoscopic findings in the infants with AC included diffuse erythema, friability, LNH and/or punctate ulcerations in 12 infants and normal appearing mucosa in 2 infants. Endoscopic findings in infants with histologically normal biopsies included erythema, ulceration and/or LNH in 2 and normal mucosa in 3. All infants with nonspecific colitis on initial biopsy had evidence of erythema, friability, ulceration and/or LNH. Our results suggest that endoscopic findings alone are not specific for AC.

Laboratory Studies

One initially recruited subject was found to have *Aeromonas* infection by stool culture and was excluded from the study. No subject was anemic. Mean serum eosinophil counts in the infants with AC were $0.88 \pm 1.15 \times 10^3/\text{mm}^3$ compared with $0.17 \pm 0.11 \times 10^3/\text{mm}^3$ in infants with normal histology ($P = 0.04$) (Fig. 2, A). The mean serum IgE level in infants with AC was 7.48 U/mL and 0.79 U/mL in normal biopsy infants. These means were statistically different after log transformation. The mean

TABLE 3. Reported symptoms at enrollment

Symptoms	AC (n = 14)	NL (n = 5)	NSC (n = 3)
Diarrhea	6	3	1
Vomiting	7	0	1
Rash	5	1	1
Wheezing	1	0	0
Constipation	0	0	0

AC, allergic colitis; NL, normal biopsy; NSC, nonspecific colitis.

natural log of the serum IgE level was 1.33 ± 1.22 in infants with AC and -0.35 ± 0.60 ($P = 0.01$) in normal biopsy infants (Fig. 2, B). Serum eosinophil counts and natural-log IgE could not be used to discriminate between infants with AC and normal biopsies.

Resolution of Bleeding

Allergic colitis. Seven of 14 infants with AC were initially formula-fed and underwent dietary change to PHF. One of these was also breast-feeding, and his mother was instructed to eliminate all cow's milk protein from her diet. Six of these 7 infants consuming PHF were followed through the 9-week study period; one was lost to follow-up after the first week. In those with complete follow-up (6), rectal bleeding resolved in 1.8 weeks (range, 1 to 5 weeks). Of those with a repeat biopsy at week 3, histology was normal ($n = 2$), improved ($n = 1$) or unchanged ($n = 1$); the parents of 2 subjects refused week 3 biopsies. The infant with unchanged histology had persistent rectal bleeding and had a diet change to LAA with resolution of bleeding by week 5 and improvement in histology by the week-6 biopsy.

Seven infants with AC were breast-feeding. One infant initially had normal histology, but was re-biopsied at week 3 because of worsening bleeding. This biopsy revealed AC, and the infant's diet was changed to PHF without subsequent improvement. The week 6 biopsy was unimproved, leading to initiation of LAA formula; bleeding resolved by week 8, and no further biopsies were performed. Of the 6 infants diagnosed with AC at the first biopsy, 1 was lost to follow-up after a week-3 biopsy that showed unchanged histology. Rectal bleeding persisted at week 3; therefore a response to PHF could not be assessed. Of the remaining 5, 2 infants had normal week 3 biopsies, 2 improved and 1 was unchanged. Although 1 of the infants with normal histology at week 3 had persistent rectal bleeding during the duration of the study, the bleeding decreased significantly, so no further dietary changes were made. Of the 5 breast-feeding infants with complete follow-up during the 9-week period and resolution of bleeding, average time to resolution was 5.6 weeks (range, 2 to 8 weeks).

Normal histology. Rectal bleeding resolved in 4 of 5 infants with normal histology in an average of 3.25 weeks (range, 2 to 5 weeks). One infant with normal

TABLE 2. Subject characteristics

	AC (n = 14)	NL (n = 5)	NSC (n = 3)
Gender (F:M)	8:6	2:3	2:1
Age at presentation (weeks)	11.4 (2–22)	10.5 (2–21)	14.7 (10–18)
Feeding at study entry			
Human milk	8 (57%)	3 (60%)	1 (33%)
Cows milk formula	3 (21%)	–	2 (67%)
Soy formula	3 (21%)	2 (40%)	–
Family history of atopy	14 (100%)	4 (80%)	3 (100%)

AC, allergic colitis; NL, normal biopsy; NSC, nonspecific colitis. Age at presentation is given as mean (range).

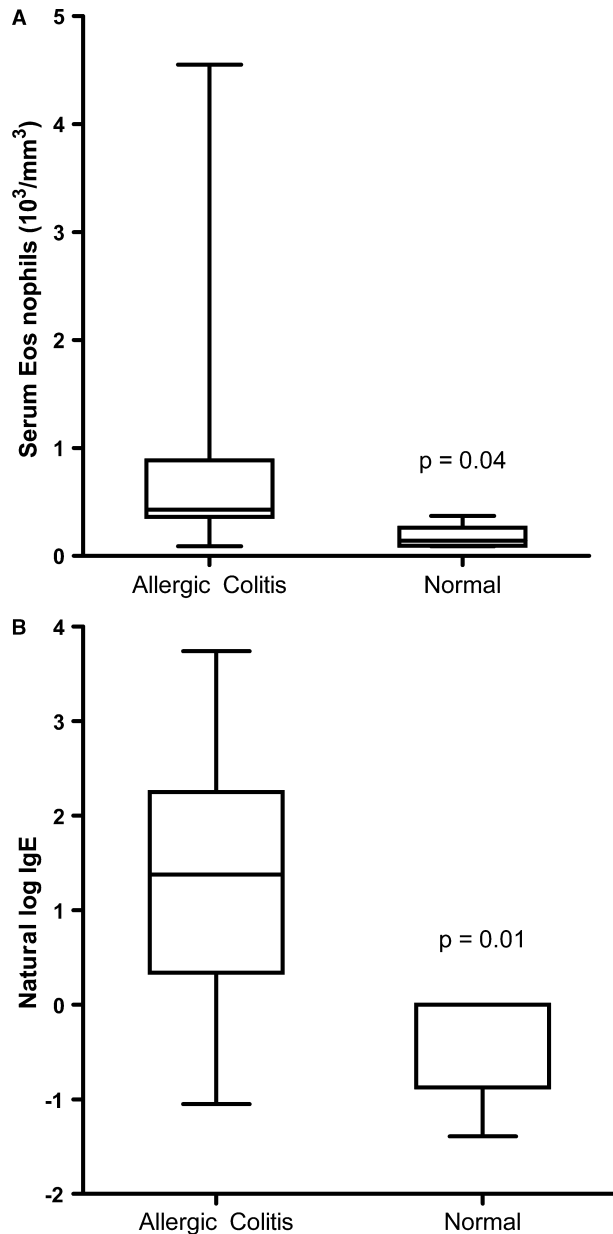


FIG. 2. A, Box plot comparing serum eosinophil counts ($10^3/\text{mm}^3$) in infants with allergic colitis and normal biopsies. B, Box plot comparing natural log of serum immunoglobulin E counts in infants with allergic colitis and infants with normal histology. Serum immunoglobulin E was not normally distributed and therefore log-transformed.

histology but continued rectal bleeding was lost to follow-up after week 3.

Nonspecific colitis. Two of 3 infants with nonspecific colitis had resolution of bleeding by week 5 or 6. The third had a family history of ulcerative colitis (mother) and continued to have persistent bleeding throughout the study. Repeat biopsy off protocol at 8 weeks demonstrated the presence of chronic colitis and cryptitis, and he

was subsequently diagnosed with infantile inflammatory bowel disease.

Survey Results

Forty-nine (88%) of 56 Ohio NASPGHAN members responded to our three-question survey of standard practice in diagnosis and treatment of presumed AC. Forty-one of 49 (83.6%) responded that they would empirically treat an infant with rectal bleeding either by changing a formula-fed infant to a hypoallergenic formula or by instructing a breast-feeding mother to eliminate all cow's milk protein from her diet. None of the gastroenterologists surveyed recommended discontinuation of breast-feeding in favor of a hypoallergenic formula as an initial intervention. Four (8.2%) would change a formula-fed infant directly to an LAA rather than PHF. Only 4 (8.2%) would confirm the diagnosis with biopsy before initiating dietary change. Forty-one (84%) of the pediatric gastroenterologists surveyed accepted the histologic definition of AC that we used in our study.

If bleeding continued for longer than 3 weeks after dietary change, 20 (40.8%) would recommend empirically changing a formula-fed infant from a PHF to LAA formula and stopping breast-feeding in favor of a PHF. However, an additional 20 (40.8%) would obtain biopsies before instituting further dietary changes. Eight (16%) would wait a further 4 to 6 weeks before further evaluation or dietary change.

DISCUSSION

Although AC is believed to be a common cause of rectal bleeding in healthy infants, the lack of a specific, noninvasive test for AC makes it difficult to calculate the true prevalence among healthy infants. The majority of cases are empirically diagnosed and treated. The lack of specific signs and symptoms of AC also complicates diagnosis (11).

The reported prevalence of cow's milk-induced allergy varies widely, ranging from 0.3% to 7.5% of all healthy infants (12, 13). Most prospective studies are limited by referral bias and small size (14, 15). In our cohort, the prevalence of biopsy-proven AC among healthy infants with rectal bleeding was 64%. Although our study is also limited by small size, we recruited subjects from pediatrician's offices, the emergency department and our clinic to minimize referral bias. However, the study design did exclude infants who already had a formula or maternal diet change as a result of the presumptive diagnosis of AC.

AC is thought to be secondary to an allergic reaction to a protein or proteins in the diet. Cow's milk contains many immunogenic proteins, of which beta-lactoglobulin is the most common antigen related to allergy (13). Soy proteins also have antigenic properties (13). It is reported

that as many as 30% of patients are allergic to both cow milk and soy protein (12). Breast-feeding does not prevent AC; in our study, half of the subjects with AC were exclusively breast-fed. In breast-fed infants, the colitis presumably results from dietary antigens transmitted through breast milk (7,10,15–17).

Current therapy for infants with AC is the elimination of suspected triggering antigens. As shown by our survey, formula-fed infants typically have been changed to a more expensive PHF or LAA. Not all infants with rectal bleeding have AC, however, and empirically treating all otherwise healthy infants with rectal bleeding as AC may lead to unnecessary and expensive formula changes. In our study, 36% of infants would have had their diet unnecessarily changed. Often these formulas are continued for the entire first year. Although our study was not designed to conduct a cost analysis, our data suggest that considerable cost savings could be achieved by decreasing unnecessary formula changes. In addition, switching to hypoallergenic formulas empirically may encourage the parents to view their child as sick or vulnerable and they may continue unnecessary dietary restrictions later in childhood (18).

In breast-fed infants with rectal bleeding, cow's milk protein is often first eliminated from the maternal diet or the infant's diet is changed to PHF. Elimination of cow's milk proteins from the diet of breast-feeding mothers is challenging and may discourage continued breast-feeding.

Our study confirms that gross endoscopic findings in healthy infants with rectal bleeding are often nonspecific and not helpful in diagnosing AC. LNH has also been described as a sign of food allergy in children (19, 20). However, in our study several infants with LNH but without histologic evidence of AC had spontaneous resolution of bleeding over a period of a few weeks with no dietary change. This suggests that LNH may be a self-limited finding associated with rectal bleeding in otherwise healthy infants. Conversely, we may have missed the diagnosis of AC because of the focal nature of eosinophilic infiltration. AC has been shown to be a very focal disease with variability both within specimens and between specimens taken from different locations in the rectosigmoid colon (10). Thus, despite taking specimens at 5, 10 and 15 cm from the anal verge, there is the possibility that we could have misclassified some cases as normal or nonspecific colitis. However, as bleeding resolved without intervention in the majority of infants with normal mucosa or nonspecific colitis, this suggests that either AC was not missed or was self-limited in some infants.

Mean peripheral blood eosinophil counts and serum IgE were statistically higher in infants with AC. These tests were not useful discriminators between infants with AC and normal histology, however, because of overlap in the ranges (5,9,14,15). Elevation of serum IgE is consistent with observations in atopic variants of other eosinophilic gastrointestinal disorders; however these are

thought to be polygenic disorders that involve both IgE-mediated and delayed T helper cell type 2 responses to allergens (21). Likewise, not all cow's milk hypersensitivity in infants is IgE-mediated (22,23). Recent reports have suggested that decreased cow's milk specific IgE levels at time of diagnosis may predict infants that are more likely to develop tolerance to cow's milk in early childhood (24,25).

We found that bleeding resolved with avoidance of cow's milk protein for the majority of infants with AC in an average of 1 to 3 weeks. There was a trend for a longer resolution period in breast-feeding infants. Only 2 infants required a change to an LAA formula because of a lack of response to PHF. In infants without AC, the majority also had resolution of their bleeding without intervention. The only exception was an infant with a maternal history of ulcerative colitis who had continued bleeding throughout the study period leading to re-biopsy at study conclusion and diagnosis of infantile inflammatory bowel disease. This suggests that close follow-up of infants will identify those who fail to respond.

We conclude that the prevalence of AC in our population-based study of healthy infants with rectal bleeding was 64%. Although the confidence interval is wide because of the difficulty in recruiting a larger cohort, these findings suggest that empiric diagnosis of AC in otherwise healthy infants with rectal bleeding may lead to unnecessary and expensive formula changes or changes in maternal diet that may discourage continuation of breast-feeding.

An important question that our study did not address is whether all infants with AC need dietary treatment or whether AC spontaneously resolves in some or all infants. It is possible that the focal nature of eosinophilic infiltration in AC may have led to misclassification of some infants in our study into the normal or nonspecific colitis groups. Resolution of bleeding without intervention occurred in the majority of infants with either normal histology or nonspecific colitis. The benign clinical course of most infants with AC and the spontaneous resolution of bleeding in the majority of infants with normal histology or nonspecific colitis suggest that a larger prospective study of outcome of bleeding without dietary change in otherwise healthy infants with AC might be warranted.

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