

DIETARY PROTEIN ENTEROCOLITIS

Alan M. Lake, MD

Adverse food reactions are commonly reported in the first several years of life, but many are poorly documented. In a prospective study of nearly 500 newborns through the first 3 years of life, however, Bock documented that 8% of the children had a reproducible response to oral food challenge, approximately 60% with diarrhea, 40% with emesis, and 20% with irritability and colicky discomfort.⁶ The majority of these reactions are to cow milk protein, with more than 80% clinically resolving by 3 years of age, and most are not IgE-mediated.¹⁶

The IgE-mediated syndromes of oral allergy, gastrointestinal anaphylaxis, and some children with eosinophilic esophagogastritis are not discussed in this article. Primarily, the non-IgE syndromes are usually defined on the basis of their clinical presentations as enteropathy (if primarily it is a malabsorption disease), enterocolitis (if emesis, diarrhea, and bleeding are prominent in an infant who is clinically ill), or proctitis (if there is mild rectal bleeding in an infant who is clinically well).²⁴ The clinical distinctions are further summarized in Table 1.

DIETARY PROTEIN ENTEROPATHY

The ability of a cow's milk-based feeding to induce a malabsorption syndrome in an infant was first described in 1905.⁴⁴ Subsequently, soy, egg, wheat, and cod proteins have been implicated as potential antigens.^{2, 23, 51} In contrast to gluten-induced celiac disease, these infants usually present at a younger age, have less severe villus injury, and

From the Department of Pediatrics, Johns Hopkins University, School of Medicine, Baltimore; and Pediatric Consultants, Lutherville, Maryland

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Table 1. NON-IgE-MEDIATED FOOD HYPERSENSITIVITIES

	Dietary Protein Enteropathy	Dietary Protein Enterocolitis	Dietary Protein Proctitis
Age at onset	1-18 mo	2 d-6 mo	2 d-3 mo
Duration	18-36 mo	9-36 mo	6-9 mo
Presentation	Indolent	Acute	Acute, mild
Failure to thrive	Moderate/severe	Moderate	No
Irritability	Mild	Moderate	Minimal
Emesis	Mild	Moderate	No
Early satiety	Moderate	Moderate	No
Diarrhea	Moderate	Severe	Mild
Rectal bleeding	Minimal	Moderate	Mild/moderate
Fecal leukocytes	No	Common	Common
Anemia	Moderate	Moderate	Mild
Protein-losing enteropathy	Moderate	Moderate	Mild
Common nutrient protein implicated	Cow's milk Soy Wheat Egg, cod	Cow's milk Soy Hydrolyzed casein Rice, nut	Breast milk Cow's milk Soy Corn, egg

outgrow the protein sensitivity, generally by 3 years of age. In Finland, the frequency of this form of enteropathy is about 20% that of true celiac disease. There is a consensus that the overall frequency of this syndrome in Europe and North America has declined over the past three decades, a decline attributed to increased breastfeeding, increased use of commercial rather than home made formula, and possibly subtle alterations in enteric bacterial flora.

The universal symptom of dietary protein-induced enteropathy is diarrhea, usually associated with early satiety, emesis, and significant failure to thrive.^{23, 51} Malabsorption investigations have revealed steatorrhea, reduced D-xylose absorption, and lactose intolerance in more than 50% of involved infants. Anemia is documented in about one third of the infants, whereas edema from protein-losing enteropathy is noted in at least 25%. The combination of reduced intake with malabsorption leads to moderately severe interference with weight gain, relative to reduced height gain. The age at presentation varies from 1 to 18 months based on age of exposure to the offending protein. It is a more "sub-acute" presentation than either enterocolitis or proctitis, evolving over several weeks.

As noted previously, cow's milk protein is most commonly implicated, although soy, egg, wheat, cod, rice, and chicken are also well described. Serum IgE, specific radioallergosorbent test (RAST), and skin tests to the protein are generally negative. Mild increases in IgA antibody to cow's milk and nonspecific lymphocyte stimulation responses have been seen.⁴² With elimination of the offending protein, clinical remission is seen in 7 to 10 days.

Small bowel biopsies reveal a patchy, usually subtotal villus injury

with increased crypt mitotic activity.^{18, 23, 32} By electron microscopy, the epithelial cells are cuboidal with short, branched microvilli and uneven thickening of the basement membrane. There is a marked increase in intraepithelial CD8+ or cytotoxic lymphocytes and a more specific increase in activated CD4+ lymphocytes in the lamina propria. Serum and tissue levels of complement are normal, both at diagnosis and with challenge. Focal edema, mast cell degranulation, and mild increases in eosinophils suggest that one component of the inflammatory response includes IgE, although no increase in IgE is noted in the blood or tissue after protein challenge.^{18, 42} Biopsies at diagnosis and following challenge contain increased gamma interferon (IFN- γ) and interleukin-4 (IL-4). Thus the consensus at this time is that the enteropathy is the result of T-cell activation with IFN- γ .

As noted previously, with identification and elimination of the offending protein from the diet, clinical remission is achieved in 7 to 10 days. On rare occasions, the severity of the edema and weight loss justifies a brief course of corticosteroid to hasten the pace of recovery. Neither total parenteral nutrition or L-amino acid-based formula is indicated for the vast majority of involved infants and toddlers. Long-term follow-up reported by Savilahti is that 80% will tolerate the offending protein by 2 years of age, with nearly 100% recovery by 3 years.⁴³

DIETARY PROTEIN ENTEROCOLITIS

Dietary protein enterocolitis is an acute clinical syndrome of enterocolitis usually presenting between 1 week and 3 months of age. The dietary proteins implicated are generally cow's milk or soy protein. Although the clinical manifestations are relatively acute, the process is not classified as an anaphylaxis owing to lack of markers of immediate hypersensitivity.

In 1940, Rubin described an infant presenting with rectal bleeding who was responsive to elimination of cow's milk from the diet.⁴¹ In 1966, Gryboski added eight infants to the literature with an inflammatory colitis responsive to cow's milk protein elimination.¹² Soy protein was first implicated by Halpin in 1977¹³ with a subsequent clinical summary and confirmatory challenge protocol described by Powell in 1978.³⁸ By 1984, Jenkins concluded that food protein was the major cause of colitis in infancy.¹⁹

Although diarrhea and emesis are the most prominent symptoms, rectal bleeding, protein-losing enteropathy with edema, and dehydration with metabolic acidosis are also prominent. Table 2 lists the major clinical manifestations, including a relatively frequent complication of transient methemoglobinemia in up to 30%.³¹

The diarrhea is relatively acute and progressive to the point of dehydration if the etiologic protein is not eliminated. The stools contain mucus, which, if stained, usually contains polymorphonuclear leukocytes and eosinophils. Rectal bleeding progresses from occult to increas-

Table 2. CLINICAL PRESENTATIONS OF DIETARY PROTEIN ENTEROCOLITIS

Symptoms	Frequency (%)
Acute, progressive diarrhea	Universal
Hematochezia	Universal
Irritability	90
Abdominal distention	75
Recurrent emesis	75
Food refusal	70
Failure to thrive	60
Protein-losing enteropathy	50
Anemia	50
Dehydration/acidosis	40
Methemoglobinemia	30

ingly gross bleeding and anemia. Whereas the diarrhea is most consistent with an inflammatory colitis, stools may also contain reducing sugars, suggesting a small intestinal component as well. Approximately one third of the infants with severe diarrhea will develop metabolic acidosis. Hypotension may complicate the presentation in younger infants but is more commonly seen following protein challenge, especially with soy. The acute nature and severity of the symptoms often lead to concerns about possible sepsis.

Irritability, emesis, and abdominal distention are also prominent with acute manifestations. When a more indolent clinical course is encountered, the infant will manifest failure to thrive, edema from enteric protein loss, and anemia. Food refusal, a feature of eosinophilic esophagitis and enteropathy, is also common.^{9, 48}

Although cow's milk and soy protein are predominantly implicated in infancy, other food proteins documented to produce an enterocolitis in childhood include egg, wheat, rice, oat, peanut, nuts, chicken, turkey, and fish.^{7, 19, 37, 47, 50} On rare occasions, enterocolitis has been encountered in infants fed extensively hydrolyzed casein-based formula.^{9, 21, 48}

The diagnostic investigations undertaken vary greatly, depending on whether the child is referred to an allergist or gastroenterologist. Regrettably, both perspectives are rarely applied to the same child. Because colitic symptoms predominate, the first procedure from the gastroenterologist is usually colonoscopy. The mucosa demonstrates patchy erythema, edema, and frequently aphthous ulceration.^{5, 19, 52} The mucosa is friable, and maximal disease is usually noted in the distal colon. Biopsies of the colon reveal superficial ulceration with acute and chronic inflammatory cell infiltration with eosinophils, lymphocytes, and mucus cell depletion. Lymphoid nodular hyperplasia is frequently noted grossly and is confirmed histologically in both the colon and small bowel. Biopsy data from the small bowel is rarely reported but may feature partial villus injury as well as lymphoid aggregates.

Involvement of the small bowel is further suggested by alterations in permeability to lactulose, with increased intercellular transport corre-

lating with degree of inflammation, although not necessarily to symptoms.⁹ Radiographic contrast studies of the small bowel feature thickened folds and diffuse edema, correlating primarily with reduced serum proteins. A barium enema will reveal spasm, superficial ulceration, lymphoid nodularity, and submucosal edema.⁴⁰ Progression to stricture of the colon has been described as has pneumatosis intestinalis.^{4, 45}

Immunologic investigation reveals that RAST-specific IgE and skin tests are negative. Increased protein-specific IgA and lymphocyte stimulation responses have been described for soy, casein and β -lactoglobulin.^{30, 49} Increased cytokine release from peripheral monocytes has recently been reported, particularly tumor necrosis factor alpha (TNF- α). Increased recovery of TNF- α has been noted in the stools of infants upon positive food challenge and, in cell culture, TNF- α combined with IFN- γ is cytotoxic to intestinal epithelial cells.

The diagnosis is confirmed when symptoms resolve within 72 to 96 hours after the elimination of the offending protein from the diet, and subsequent oral challenge provokes both symptoms and a measurable inflammatory response. The oral food challenge is based on the observations of Powell³⁸ as recently reviewed by Sicherer.⁴⁷ With open challenge, a dose of 0.15 to 0.6 g of protein per kilogram of body weight is given, with the dose chosen based on the severity of the presenting symptoms. Patients remain under direct observation for 6 to 8 hours as increasing doses are delivered. Peripheral blood counts are obtained as a baseline and at four to six hours after the challenge. A positive response usually features the onset of emesis and diarrhea within 1 to 6 hours and an increase in the absolute poly count of at least 3500 cells/mm³. A modest number of patients, especially those with soy protein-induced enterocolitis, will have severe reactions to food challenge manifesting as intractable emesis, dehydration, and hypotension requiring intravenous fluid therapy.

More than 90% of the infants will respond to initiation of an extensively hydrolyzed casein-based formula.^{14, 22} From 15% to 50% of infants sensitive to cow's milk will also be sensitive to soy-based formula.²² Indeed, multiple formula intolerance is commonly reported.¹⁷ Approximately 10% of involved infants do not respond to the use of extensively hydrolyzed formula and require the use of an L-amino acid-based product.^{9, 17, 48} The long-term responses to open food challenge suggest that 50% of involved infants can tolerate the offending protein by 18 months of age and 80% by age 3 years. Again, infants sensitive to soy take longer to tolerate the protein; a number of the author's patients are still positive to food challenge past 7 years of age. A number of these older children with "atypical" enterocolitis will develop positive skin and RAST-specific IgE, suggesting the "acquisition" of food allergy.⁴⁷

DIETARY PROTEIN PROCTITIS

Over the past 20 years, a group of infants have been reported to present with bloody stools but with far more benign enteric and systemic

features than infants with classic dietary protein enterocolitis. In these reports, this condition has been referred to as allergic colitis, benign dietary proctocolitis, eosinophilic proctitis, or breast milk proctocolitis. Originally described in breastfed infants,²⁵ it has subsequently been seen in infants fed cow's milk formula, soy formula, and even extensively hydrolyzed protein formulas.^{8, 11, 20, 28, 33, 35, 36, 53, 54} In contrast to the other non-IgE-mediated enteric syndromes, more than half of the reported infants have been extensively if not exclusively breastfed.

Typically, the infants present at 2 to 6 weeks of age with blood streaked soft to normal stools, with a range from 2 days to 3 months. Weight gain and growth are normal ("aside from the diaper, the child is well"). Neither emesis nor abdominal distention are seen. Perianal examination may reveal a small internal rectal fissure caused by spasm with evacuation of stool, which, over several weeks may be associated with some discomfort. The rectal bleeding is usually not grossly apparent in every stool, although tests for occult blood are consistently positive. The smear of the mucus in the feces generally demonstrates increased numbers of polymorphonuclear cells. In contrast, Odze reported that the smear for eosinophils is usually negative.³³ Stool cultures are negative for pathogenic bacteria.

In the only systematic review of the laboratory findings in these infants, Machida demonstrated a mild peripheral eosinophilia and hypoalbuminemia in most of the infants.²⁸ Anemia develops over several weeks but is rarely of clinical concern.^{25, 35} Radiographic investigations are rarely performed, aside from a desire to exclude necrotizing enterocolitis or the enterocolitis of aganglionic disease.

Limited colonoscopic examinations have revealed inconsistent gross features ranging from focal erosions to linear erosions and friability, which may be prominent in the sigmoid colon, even when the rectum is relatively spared.¹⁰ The presence of nodularity and focal erosions frequently suggests lymphoid nodular hyperplasia. No investigations of the esophagus, stomach, or duodenum have been reported. In infants with more chronic symptoms at presentation, the gross features of inflammatory ulceration are more prominent.²⁵ There is no correlation between the gross features and the nutritional history of the infant.

Although the endoscopic features are highly variable, the microscopic inflammation is highly consistent. There is an acute inflammatory response with striking eosinophilic infiltration of the epithelium, lamina propria, and often the muscularis. These features can be focal, even within a single biopsy.³⁴ Eosinophil counts in excess of 10 to 20 per high-powered field are common. Focal epithelial erosions are common, whereas forked crypts and other chronic inflammatory features are rare. Nodules of lymphoid aggregates are often seen with eosinophils penetrating the rim. Although giant cells have been reported, granuloma formation is not.³⁹

As with the other non-IgE-mediated syndromes, the elimination of the offending protein from the infant's diet leads to a clinical resolution within 72 to 96 hours, which is true in both formula and breastfed

infants. The exclusion must be rigorously complete. Most infants respond immediately to the use of an extensively hydrolyzed formula. When rechallenged in the first 6 months of life, nearly all resume bleeding within 72 hours. In contrast to enterocolitis, no peripheral blood leukocytosis is seen. By 9 months of age, nearly all of these infants will tolerate an unrestricted diet. In a long-term follow-up of 100 infants with proctocolitis for more than 10 years, Hill reported no long-term concerns.¹⁵

The breastfed infant, a unique feature of this syndrome, is usually managed with continued nursing on a maternally restricted diet. By process of elimination and rechallenge with maternal dietary proteins, cow's milk is the offending antigen in more than 50% of cases. Indeed, in a 16-year experience in 95 breastfed infants with proctitis, the implicated protein was cow's milk in 62 infants, egg in 18, corn in 6, and soy in 3, with multiple antigens in only 5.

In 11 of the 95 infants, bleeding persisted despite rigorous efforts to identify an offending protein in the nursing mother's diet. To document the syndrome, seven cleared on hydrolyzed casein formula, whereas four cleared only with use of an L-amino acid formula. Of note, these four also were somewhat older, had longer duration of symptoms before intervention, and also had eczema. Ten of these eleven infants resumed and continued breastfeeding even in the face of ongoing low-grade bleeding. An additional 11 nursing mothers could not maintain a strict elimination of the offending protein. These 21 infants were followed for more than 6 months with no significant progression of inflammatory concern, although six became mildly anemic despite iron supplementation. All of the breastfed infants, as with the formula-fed infants, tolerated an unrestricted diet by 1 year of age.

In 1921, Shannon demonstrated that maternal dietary protein was transported antigenically intact through human breast milk.⁴⁶ More recent investigations confirm the presence of bovine β -lactoglobulin throughout lactation.^{3, 27, 29} The ability of microgram doses to induce anaphylaxis in a breastfed infant has also been shown.²⁶ Although no systematic investigation has proven that the inflammatory response in these infants is restricted to the lower colon, it is assumed in the breastfed infant that the antigen is released from an antibody or physical complex by the enteric flora or environment of the lower rectum allowing disease activity at that level.

The pathogenic role of the eosinophil has also not been defined in this context. The eosinophil is considered a pro-inflammatory cell with receptors for IgA as well as IgE.¹ The eosinophil may also be a generic component of the immature immune system of the neonate because it is noted in erythema toxicum and even reflux esophagitis.

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Address reprint requests to

Alan M. Lake, MD
 Pediatric Consultants
 10807 Falls Road, Suite 200
 Lutherville, MD 21093