

## ABM Clinical Protocol #24: Allergic Proctocolitis in the Exclusively Breastfed Infant

The Academy of Breastfeeding Medicine

*A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient. These guidelines are not intended to be all-inclusive, but to provide a basic framework for physician education regarding breastfeeding.*

### **Purpose**

**T**HE PURPOSE OF THIS clinical protocol is to explore the scientific basis, pathologic aspects, and clinical management of allergic proctocolitis in the breastfed infant as we currently understand the condition and to define needs for further research in this area. Although there can be a variety of allergic responses to given foods, this protocol will focus on those that occur in the gastrointestinal tract of the breastfed infant, specifically allergic proctocolitis.

### **Definitions**

- Exclusive breastfeeding: The infant has received only breastmilk from the mother or expressed breastmilk, and no other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements, or medicines.<sup>1,2</sup>
- Food allergy: An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.<sup>3</sup>

### **Background**

Over recent decades, a group of exclusively breastfed infants has been described that develop bloody stools but are otherwise well appearing. This entity has carried a number of titles ranging from allergic colitis to benign dietary protein proctitis to eosinophilic proctitis to breastmilk-induced proctocolitis.<sup>4</sup> Herein this appearance is referred to as allergic proctocolitis in the exclusively breastfed infant, and knowledge of the clinical course and factors associated with the development of this entity are essential to optimize breastfeeding success and to support the growth and overall health of the infant.

### **Incidence**

The incidence of adverse reactions to food proteins in the exclusively breastfed infant is poorly defined. Prospective

data indicate approximately 0.5–1% of exclusively breastfed infants develop allergic reactions to cow's milk proteins excreted in the mother's milk.<sup>5</sup> Given that cow's milk protein is the offending antigen in 50–65% of cases,<sup>4,6</sup> the total incidence of food allergy in the exclusively breastfed infant appears slightly higher than 0.5–1%. Comparatively, infants fed human milk appear to have a lower incidence of allergic reactions to cow's milk protein than those fed cow's milk-based formula.<sup>7</sup> This may be attributable to the relatively low level of cow's milk protein excreted in human milk,<sup>8</sup> immunomodulatory substances present in human milk, and/or differences in the intestinal flora between breastfed and formula-fed infants.<sup>9–12</sup>

### **Clinical presentation**

The most common symptoms associated with food-induced allergic disorders in the exclusively breastfed infant are cutaneous reactions (eczema) and gastrointestinal symptoms.<sup>5</sup> Severe manifestations of food allergy are extremely rare. The most common gastrointestinal symptom is the development of bloody stools.<sup>13–15</sup> This usually occurs between 2 and 6 weeks of age,<sup>6</sup> although some have reported symptoms beginning as early as the first day of life.<sup>16,17</sup> Dietary proteins excreted in the mother's milk are responsible for the majority of cases and induce an inflammatory response of the rectum and distal sigmoid colon referred to as allergic proctocolitis.<sup>18</sup> It should be emphasized that breastfed infants with allergic proctocolitis are generally "well appearing" other than the presence of blood within the stool. Blood loss is typically modest but can occasionally produce anemia and/or hypoalbuminemia. In very rare cases, symptoms may lead to failure to thrive.<sup>19–21</sup> Systemic manifestations such as emesis, dramatic diarrhea, or abdominal distention are rare and may suggest other allergic disorders of the gastrointestinal tract such as food protein-induced enterocolitis or enteropathy (not reviewed in this protocol).

Additional laboratory studies may be considered but are often unnecessary to make the diagnosis of allergic

proctocolitis. Peripheral eosinophil counts may be elevated; however, this is poorly indicative in an individual patient.<sup>21-23</sup> A fecal smear looking for an increased number of eosinophils is often reported negative.<sup>18</sup> If the fecal smear does not contain detectable leukocytes, it is not suitable for mucosal cytology, and the report of no eosinophilia is not reliable (T. Takamasu, personal communication, June 9, 2011). Stool cultures are negative for pathogenic bacteria, and radiographic studies exclude necrotizing enterocolitis.<sup>6,24</sup> Total and antigen-specific serum immunoglobulin E concentrations are similar to those of non-affected infants and thus need not be measured.<sup>13</sup> In severe or protracted cases unresponsive to dietary modification, endoscopic evaluation may be warranted.

### Pathophysiology

The symptoms and severity of food hypersensitivity vary according to the mechanism of immune response (immunoglobulin E vs. cell-mediated) and location of intestinal involvement.<sup>6,25</sup> Allergic proctocolitis in the breastfed infant is a cell-mediated hypersensitivity disorder of the distal large bowel characterized by mucosal edema, focal epithelial erosions, and eosinophilic infiltration of the epithelium and lamina propria.<sup>14,18,19,26,27</sup> Biopsy specimens typically demonstrate eosinophil counts of greater than 20 per high-powered field.<sup>21,28,29</sup> The passage of dietary proteins into maternal milk is responsible for the majority of cases,<sup>30</sup> and elimination of the offending agent from the maternal diet usually results in cessation of symptoms within 72–96 hours.<sup>6</sup> In some cases, dietary restriction for up to 2–4 weeks may be required to notice improvement.<sup>12,31</sup> In a published series of 95 breastfed infants with bloody stools, 65% were determined to be attributable to maternal ingestion of cow's milk, 19% to egg, 6% to corn, and 3% to soy.<sup>4,6</sup>

It remains unclear when the sensitization phase of allergic proctocolitis occurs. Some infants have been reported to respond adversely to food proteins excreted in the mother's milk within the first day of life.<sup>16,17</sup> It is apparent that dietary and environmental antigens are capable of crossing the placental barrier<sup>32</sup> or entering the amniotic fluid,<sup>33</sup> which is swallowed by the fetus. These findings suggest the possibility of in utero sensitization following maternal antigen exposure during pregnancy.<sup>34</sup> Alternatively, variations in the concentration of several immunomodulatory substances in human milk appear to influence the protective effect of breastfeeding against allergy.<sup>35-38</sup> Human milk contains viable leukocytes that may play a role in antigen processing and presentation to neonatal lymphocytes in the intestine.<sup>39,40</sup> Thus, it is possible that ingestion of dietary food proteins excreted in the mother's milk, accompanied by physiologic conditions favoring immunogenic responses (in the neonate or maternal milk), may result in allergic sensitization. At present, however, there are insufficient data to recommend dietary restriction during pregnancy and/or lactation as a means of allergy prevention.<sup>3,41</sup> Breastfeeding should be encouraged in all neonates, even though small quantities of food allergens may be present within the milk. Indeed, recent data in animal models suggest that ingesting small quantities of allergens excreted in the mother's milk in the presence of the anti-inflammatory cytokine transforming growth factor- $\beta$  may actually protect offspring against subsequent allergic responses to that same allergen later in life.<sup>42-44</sup>

### Maternal Elimination Diet

When an exclusively breastfed baby has clinical evidence of allergic colitis, the first line of treatment is the maternal elimination diet, avoiding food containing the most likely allergen, cow's milk protein. Having a rigorous diet imposed can be extremely hard for a new mother, who is dealing not only with being a new mother and breastfeeding, but also with her concerns for her baby's symptoms.

#### Elimination diet plan

Several different methods are proposed:

1. To make it as simple as possible, one can start by eliminating the most likely suspects for allergies one at a time (i.e., cow's milk [and products made with cow's milk like cheese, butter, ice cream, and other dairy products], soy, citrus fruits, eggs, nuts, peanuts, wheat, corn, strawberries, and chocolate). Mothers are instructed to eliminate one food or food group (e.g., dairy products) at a time and wait a minimum of 2 weeks and up to 4 weeks. Most cases will improve within 72–96 hours.<sup>6</sup>
2. If there have been no changes with the infant's symptoms in that time, the mother can usually add this food back into her diet and eliminate another food or food group from the list. This continues until she has eliminated all of the foods listed. When eliminating a food, she also needs to remember to eliminate any other foods that contain this product (i.e., when eliminating cow's milk, eliminate anything made with cow's milk, not forgetting the specific protein components like casein, whey, lactoglobulin, etc.; it is important to read labels for these other component ingredients). Often mothers don't think about the fact that other foods contain these products. The Summary of the United States Expert Panel suggests that individuals with food allergy and their caregivers receive education and training on how to interpret ingredient lists on food labels and how to recognize labeling of the food allergens used as ingredients in foods; the Expert Panel also suggests that products with precautionary labeling, such as "this product may contain trace amounts of allergen," be avoided.<sup>3</sup> Don't forget that some medications, vitamins, and even vaccines may have allergenic ingredients.
3. If eliminating each of these foods does not solve the problem, the next step could be to have the mother keep a very complete food diary for 2 weekdays and 1 weekend to see what her usual eating habits are. By carefully reviewing her food diary, one may be able to pinpoint the offending food.

#### Geographic differences

Others recommend eliminating the most likely causes of allergies, cow's milk protein, and any other likely allergens based on the region in which the baby lives.<sup>12</sup> For example, in some regions, hen's eggs are the second most common cause of allergy, whereas in others, like the United States, the United Kingdom, and some areas of Europe, peanuts are a common allergen.<sup>12</sup>

### Difficult Cases

Moving further to a diet that also excludes fish, wheat, and other gluten-containing grain products is very difficult for a mother to follow and may increase her risk of consuming an unhealthy diet. The maternal risks of an extensively restrictive elimination diet must be weighed against the potential infant benefits. In a secondary approach, the additional elimination of wheat and fish and/or other significant parts of a mother's diet should require the advice of an experienced dietician to ensure that an adequate nutritional intake is maintained.<sup>12</sup>

For babies with more significant symptoms, one can place the mother on a very low-allergen diet of foods like lamb, pears, squash, and rice. Again, this approach requires ongoing consultation with an experienced dietician. When the baby's symptoms resolve, other foods are added back to the mother's diet one at a time, with sufficient time between additions (minimum of 1 week) to look for recurrence of symptoms in the baby. If symptoms recur, that recently added food is removed again and is likely the offending food. Other foods may also be incriminated. Continuing to add foods in one at a time allows the mother to liberalize her diet if the baby tolerates it.

### Use of Pancreatic Enzymes

There have been a few published reports<sup>45,46</sup> and some anecdotal discussions of a novel treatment for allergic colitis—the use of pancreatic enzymes by the mother. The theory is that by giving the mother exogenous pancreatic enzyme, the protease component will help further break down the potential protein allergens in the mother's gastrointestinal tract, before they are absorbed into her bloodstream and secreted into her milk. Specific dosing has yet to be defined, but generally one starts with the lowest dose of pancreatic enzyme (e.g., pancrelipase Creon<sup>®</sup> 6 [in United States]/Kreon<sup>®</sup> [Europe], Abbott Laboratories, Abbott Park, IL) (the strength is based on the lipase content, in this case 6,000 USP units of lipase; it also contains 19,000 USP units of protease and 30,000 USP units of amylase) so as to minimize, although rare, any side effect to the mother. The dose can begin as two capsules with meals and one with snacks and be doubled if the desired effect is not achieved. The use of proprietary enzymes that are pork-derived should be avoided in persons allergic to this allergen. There are alternative plant-derived enzymes, but the dosing is less clear as their comparative potency is difficult to ascertain (A. Repucci, personal communication, May 1, 2011). Reports are generally positive with this approach. This is usually in addition to the elimination diet and can be used in situations where food ingredients may not be known for sure, as in foods consumed at a restaurant.

### Evaluation and Management

Quality of evidence for each recommendation, as defined in the U.S. Preventive Task Force guideline,<sup>47</sup> is noted in parentheses (I, II-2, and III).

The initial evaluation of the exclusively breastfed infant with bloody or occult heme-positive stools should include a comprehensive history and physical examination:

- Particular emphasis should be directed towards a strong family history of allergy (biological parent or sibling), which places the infant at high risk for developing allergy.<sup>3,12,41</sup>
- Assurance of the exclusive nature of human milk feeding is important because the management strategies differ for breastfed and formula-fed infants.
- Evaluation for additional symptoms of food-induced allergic disorders is necessary. Many infants with allergic proctocolitis will also exhibit cutaneous reactions (eczema).<sup>5</sup>
- Accurate assessment of growth (weight and length gain), heart rate, and respiratory rate should be undertaken.
- Performance of a thorough abdominal examination. Infants with allergic proctocolitis are generally “well appearing,” non-distended, and non-tender.
- Inspection for a perianal fissure or significant rash.
- Laboratory evaluations are generally unnecessary; however, in cases of suspected moderate to severe allergic proctocolitis, one may consider obtaining a hemoglobin level to screen for blood loss and serum albumin, which decreases in protein-losing enteropathy.

### Recommendations

1. If severe allergic proctocolitis is suspected based on any of the following:
  - Failure to thrive
  - Moderate to large amounts of blood in the stool with decreasing hemoglobin
  - Protein-losing enteropathy
    - i. The infant should be referred to a pediatric subspecialist (allergist or pediatric gastroenterologist) for diagnosis and treatment. (III)<sup>47</sup>
    - ii. While awaiting the appointment, begin an elimination diet in the mother, continuing her daily vitamins as suggested for all breastfeeding mothers and adding calcium supplementation (1,000 mg/day divided into several doses).<sup>12</sup> (See Maternal Elimination Diet, above). (II-2)<sup>47</sup>
    - iii. In the majority of patients, it is reasonable and safe to continue breastfeeding through the elimination process while awaiting the appointment and thus to protect breastfeeding. However, if the hemoglobin or albumin level is significantly low (based on age-dependent published norms), the use of a hypoallergenic formula may be considered (III).<sup>47</sup>
2. If mild to moderate allergic proctocolitis is suspected based on the following:
  - Blood-positive stool or small amounts of visible blood in stool).
  - Weight gain and growth are normal.
  - Abdominal exam is benign; no abdominal distention or recurrent vomiting.
  - Stable hemoglobin and albumin levels (if measured).
    - i. The infant should continue breastfeeding. The mother should be started on an elimination diet, continue her daily vitamins as suggested for all breastfeeding mothers, and add calcium supplementation (1,000 mg/day divided into several doses).<sup>12</sup> (II-2)<sup>47</sup>
    - ii. The elimination diet trial for any given food or food group should be continued for a minimum of 2 weeks and up to 4 weeks. Most cases will improve within 72–96 hours.<sup>6</sup> (II-2)<sup>47</sup>

3. In cases of suspected mild to moderate allergic proctocolitis with improvement in response to maternal elimination diet:
  - Consider reintroducing the allergen back into the mother's diet. (I)<sup>47</sup>
  - If symptoms recur, the suspected food should be eliminated from the mother's (and infant's) diet until 9–12 months of age *and* for at least 6 months.<sup>12,13,48</sup> (II-2)<sup>47</sup> Most babies/children will tolerate the offending allergen in the diet after 6 months "from the time of diagnosis" if at least 9 months old. For example, if a baby is diagnosed at 2 weeks, the food should be avoided until 9–12 months of age. If in the rare circumstance that a baby develops allergic colitis at 5–6 months of age, the caregivers should wait a full 6 months (after diagnosis) to re-introduce, therefore at least 12 months of age, not at 9 months of age, or until the mother decides to wean, whichever comes first.<sup>12,13,48</sup> (II-2)<sup>47</sup>
4. In cases of suspected mild to moderate allergic proctocolitis with no improvement in response to maternal elimination diet:
  - Consider eliminating other allergens. (II-2)<sup>47</sup>
  - Breastfeeding may continue with monitoring of weight gain and growth. (II-2)<sup>47</sup>
  - Consider following hemoglobin and albumin levels if continued moderate degree of blood loss (blood is visible) in stools. (II-2)<sup>47</sup>
  - Consider use of pancreatic enzymes for the mother. Dosage is generally one or two capsules with snacks and two to four with meals as needed dependent on the baby's symptoms (see Use of Pancreatic Enzymes above).<sup>45,46</sup> (III)<sup>47</sup>
  - In severe cases with impaired growth, decreasing hemoglobin level, or decreasing serum albumin level, the use of a hypoallergenic formula may be considered; however, one should consider referral to a specialist. (III)

### Suggestions for Areas of Future Research

#### 1. Determine the current incidence of allergic colitis in exclusively breastfed infants

Most available epidemiologic data are from over 20 years ago, and we know the incidence of other atopic diseases (e.g., asthma) has increased over the past few decades. In addition, the results of many studies on allergic colitis in breastfed infants are complicated by the inclusion of infants who received cow's milk formula in addition to breastmilk. It would also be interesting to look at familial patterns such as what is the risk of this happening with the same mother in a subsequent pregnancy.

#### 2. Determine the influence of maternal or neonatal immunity on development of allergic proctocolitis

It is clear that antigens ingested by the mother and transferred via the milk to breastfeeding infants are responsible for the clinical manifestations of allergic proctocolitis. However, it is uncertain if the fetus is sensitized to these antigens during pregnancy or as a newborn through repeated exposure within human milk. The precise contribution of maternal immune

factors transmitted to progeny during pre- and/or postnatal life on the development of allergic responses in the neonate is also unclear. Additional investigation is needed to define the immunologic mechanisms involved in the context of specific genetic, developmental, and environmental factors in the mother and infant. Further insight into these factors would allow more focused efforts at prevention.

#### 3. Determine the safety and efficacy of maternal pancreatic enzyme use in alleviating the symptoms of allergic colitis, and if efficacious, under what circumstances they should be used

Current data are either anecdotal or in a small case study that maternal pancreatic enzyme use is both safe and efficacious. If this is shown in larger-scale studies, one would want to determine if this adjunct to maternal elimination diet should be used only as the last resort, when the elimination diet is not efficacious, or possibly as an earlier adjunct, to make the diet less onerous for the mother to follow.

#### 4. Should breastfed infants with a history of allergic proctocolitis delay or avoid exposure to other major food allergens in an attempt to prevent the development of additional food allergies?

Because young children with allergic reactions to cow's milk protein have an increased risk of developing other food allergies,<sup>49</sup> it was previously recommended that major food allergens such as peanuts, tree nuts, fish, and shellfish be avoided until at least 3 years of age.<sup>50</sup> At present, there is no evidence to conclude that this approach will be successful in preventing future allergy. Thus, consistent with recent published guidelines for the diagnosis and management of food allergy in the United States,<sup>3,41</sup> breastfed infants with a history of allergic proctocolitis should not be limited in their exposure to other major food allergens. Infants and breastfeeding mothers should only avoid the allergen identified during maternal elimination diets until 9–12 months of age and for at least 6 months. This is an active area of current research, and additional studies may provide more substantial evidence to support or change these recommendations. (III)<sup>47</sup>

#### 5. Determine the utility of additional laboratory tests for the diagnosis of allergic proctocolitis

Laboratory tests may be considered but are often unnecessary to make the diagnosis of allergic proctocolitis. In one recent case report, an infant who developed hematochezia associated with the feeding of cow's milk formula was found to have selective elevation of serum interleukin 5 (a T-helper cell type 2 cytokine).<sup>51</sup> At present, it remains unclear if serum measurements of inflammatory cytokines would be helpful for the diagnosis of allergic colitis in the exclusively breastfed infant.

### Acknowledgments

This work was supported in part by a grant from the Maternal and Child Health Bureau, U.S. Department of Health and Human Services. Thanks to Lisa H. Akers, M.S., and Jeanne Blankenship, M.S., from the American Dietetic Association for helpful suggestions and insights.

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- ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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