

Cow's Milk Allergy: A New Approach Needed?

In this issue of *The Journal*, Canani et al¹ present 2 interesting and provocative findings. First, comparing the acquisition of oral tolerance to milk protein at age 12 months, in infants fed different formulas (extensively hydrolyzed casein formula [EHCF], EHCF plus *Lactobacillus* GG [EHCF + LGG], and hydrolyzed rice, soy, and amino acid formulas), 78.9% of infants fed EHCF + LGG vs 43.6% of infants fed EHCF alone, and only 18.2% of infants fed amino acid formula (AAF) acquired tolerance. The authors conclude that EHCF accelerated tolerance acquisition, which is augmented by the addition of LGG. Second, the poor acquisition of tolerance after AAF use was striking and definitely warrants further evaluation.

Food allergy in general is considered a manifestation of failed oral tolerance induction resulting from complex interactions among gut permeability, bacterial colonization, and timing of antigen exposure. An estimated one-quarter of American households alter their diets because of a perceived food allergy.² Cow's milk allergy (CMA) is the most common food allergy in early childhood, with an incidence of 2%-3% in infants worldwide.¹ In response to the high prevalence of CMA, unclear diagnostic criteria, and variable management strategies, in 2012 the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition published guidelines for diagnosis and management of CMA.³ These guidelines, although helpful in presenting standards of care for CMA, do not include recommendations for the use of probiotics, as Canani et al have suggested. The guidelines note that probiotics/prebiotics do not have a role in the treatment of CMA, but may have a role in the primary prevention of allergy. Clinically, this issue arises during infancy, when there is no definitive way of differentiating IgE-mediated and non-IgE-mediated CMA, owing to significantly overlapping presentations; 60%-70% of infants with CMA have IgE-mediated disease, and clinical presentation can be highly variable. Onset of manifestations of CMA after exposure to milk protein can range from rapid (ie, minutes to 2 hours) to delayed (ie, 2-7 days). Generally, early onset of symptoms suggests an IgE-mediated mechanism of action, whereas delayed onset suggests a non-IgE-mediated mechanism. CMA can affect many different organ systems (Table). Certain symptoms, such as angioedema or wheezing, may suggest an IgE-mediated process, whereas gastrointestinal symptoms most likely indicate a non-IgE-mediated process.¹⁰

See related article, p ...

The diagnosis of CMA must be confirmed or excluded by an allergen elimination and challenge procedure. Specific IgE and skin prick testing alone, although helpful in identifying patients more likely to have an immediate reaction to cow's milk protein and those with a delayed reaction who are more likely to remain intolerant for a longer period, does not diagnose all cases of CMA.

In the future, atopy patch testing may be a helpful test for patients with negative cow's milk protein-specific IgE level and high clinical suspicion; however, current data are insufficient to support its routine clinical use in diagnosing CMA, and standardization is lacking. With allergen elimination/challenge as the mainstay for diagnosis, there likely is both a significant overdiagnosis and underdiagnosis of CMA. This can lead to inappropriate diets, escalating medical expenses, interference with growth, decreased quality of life, and an overall misconception surrounding food allergies in the public eye.

Management of CMA requires a balancing act between avoiding allergens and promoting acquisition of tolerance. It has been suggested that probiotics have a role in ameliorating, preventing, and accelerating acquisition of tolerance to a food allergen. This idea is becoming increasingly popular, and investigators have begun to define the role of probiotics in allergic diseases and even map their mechanisms of action. In a review of the use of probiotics in the development and treatment of allergic disease, Isolauri et al⁴ noted that probiotics may play a role in helping the gut strike a balance between mounting a brisk immune response to pathogenic antigens vs hyporesponsiveness to harmless ones, by augmenting the gut microbiota. This balance conferred on the host would allow for control of the immune response and potential induction of tolerance.

Nature already has shown us that there is a role for probiotics. Human milk transmits bacteria to the infant gut, and the oligosaccharides in breast milk, which travel undigested to the colon, are used by specific organisms in the infant gut microbiota.⁵ Thus, human milk itself influences the composition of the gut's bacterial community by selectively promoting growth via nutritional support. Furthermore, maternal probiotic supplementation during pregnancy and breastfeeding has been shown to reduce the risk of eczema in high-risk infants (ie, infants of mothers with allergic disease and atopic sensitization).⁶

Canani et al report a significant increase in cow's milk protein tolerance in the subset of patients receiving EHCF + LGG. Conversely, Hol et al,⁷ in a double-blind randomized

AAF	Amino acid formula
CMA	Cow's milk allergy
EHCF	Extensively hydrolyzed casein formula
LGG	<i>Lactobacillus</i> GG

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Table. Signs and symptoms of CMA in infants

Gastrointestinal	Respiratory	Dermatologic	General
Dysphagia	Rhinorrhea	Urticaria*	Anaphylaxis*
Regurgitation	Wheezing*	Atopic eczema	
Irritability	Chronic cough	Angioedema*	
Vomiting*			
Anorexia, feeding refusal			
Poor weight gain			
Diarrhea			
Constipation			
Hematochezia			
Iron-deficiency anemia			
Occult blood loss			

*Symptoms are most often seen immediately after exposure and associated with IgE-mediated disease.

placebo-controlled study, found no difference between patients receiving probiotics + EHCF versus those receiving placebo + EHCF. The design of that 2008 study was stronger than that of the prospective study of Canini et al, however; moreover, different strains of *Lactobacillus* were used in the 2 studies (CRL431 and Bb12 in the former, LGG in the latter). These different strains might account for the discrepant results. On the other hand, the data of Canini et al are supported by the results of a small study by Baldassarre et al,⁸ in which 30 infants with hematochezia and presumed allergic proctocolitis were evaluated using fecal calprotectin as a marker of inflammation. The authors reported a greater decrease in fecal calprotectin levels after 1 month of therapy in infants receiving EHCF + LGG compared with those receiving EHCF alone. This finding suggests an advantage from the addition of LGG, although the authors did not measure the rate at which tolerance was achieved. Given these differing results, further investigation on the role of probiotics in CMA is needed before clinical practice recommendations are made for probiotic use.

It has been shown that food allergen avoidance actually can potentiate the development of food allergies later in life. Katz et al,⁹ in a prospective study of 13 019 infants, found a significant increase in the rate of IgE-mediated CMA in patients exposed to cow's milk protein at >15 days of life compared with those exposed to cow's milk protein before 15 days of life (OR, 19.3; $P < .001$). Thus, the poor acquisition of tolerance seen in patients receiving AAF, although disconcerting, is not surprising. The recommended practice of using EHCF before AAF in patients with CMA has become widespread, based on its tolerability and cost factors, but Canini et al suggest that this actually may promote tolerance—a finding that calls for additional direct comparisons.

Formula choice is of paramount importance in children with CMA. Primary care physicians and physician extenders often make “lateral moves” from one milk-based formula to another. The role of AAF likely is quite limited compared with the prevalence of its use. AAF should be reserved for patients with severe anaphylaxis, with severe enteropathy (indicated by hypoprotei-nemia), or who fail EHCF. The use of partially hydrolyzed formulas is not recommended in CMA. On the other hand, the large majority of patients with CMA tolerate EHCF well.

Striking the proper balance between allergen avoidance and tolerance acquisition may well be best achieved by the use of EHCF. Suggestions have been made regarding the role of probiotics, specifically LGG, in the acquisition of tolerance; however, further studies comparing different strains are needed. Correct diagnosis and timely reintroduction of cow's milk protein is important for many reasons. A response to milk avoidance and milk challenge is required for diagnosis and evaluation of tolerance acquisition, respectively. Milk challenges to determine acquisition of tolerance can be performed at home for patients with gastrointestinal manifestations of CMA, unless the patient exhibits immediate hypersensitivity symptoms, in which case the challenge should be performed in the hospital or office setting.

The report by Canani et al should galvanize researchers in allergy and gastrointestinal disciplines to continue collaborating on ways to further address treatment challenges, including studies addressing formula use and the safety and role of probiotics for CMA. The development of Food Allergy Centers has come at the right time and enables patient evaluation by allergists, gastroenterologists, and nutritionists in a team approach, which can help guide primary medical providers and families in managing these children. ■

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