Interventions for Cow's Milk Allergy in Children and Infants

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Expanded Commentary from the Faculty

Acronyms:

AAF, amino acid formula
CMA, cow's milk allergy
CMP, cow's milk protein
EHCF, extensively hydrolyzed casein formula
ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FA, food allergies
IgE, immunoglobulin E
kDa, kilodalton
LGG, *Lactobacillus rhamnosus* GG
OFC, oral food challenge
SKP, skin-prick tests

Common Causes of Cow's Milk Allergy in Infants

Due to its very early introduction, cow's milk allergy (CMA) is one of the earliest identified and most common food allergies, affecting 2% to 3% of young children living in western countries.[1] Cow's milk allergy represents a failure in the mechanisms of immune tolerance, leading to an aberrant immune-mediated reaction against cow's milk proteins (CMP). CMA is now recognized as one of the first indicators of a dysregulation of the immune system in early life. According to the current view, CMA derives from a negative gene/environment interaction leading to dysfunction of the immune system that is mediated—at least in part—by modification of gut microbiota composition and function, and by epigenetic mechanisms.[1]

Symptoms of Cow's Milk Allergy

The clinical signs and symptoms of CMA are numerous; they depend mainly on the underlying immune mechanism. Infants with IgE-mediated CMA could present with severe anaphylaxis, urticaria, vomiting, and/or respiratory symptoms. Respiratory conditions can include sneezing, nasal congestion or rhinorrhea, stridor derived from upper airway obstruction, and/or wheezing.[1,2] Separately, infants affected by non-IgE-mediated CMA present mainly with gastrointestinal symptoms and/or atopic dermatitis, which may include a rash and/or itching.[2]

Testing for Cow's Milk Allergy

The diagnosis of CMA is a multistep process that includes a full anamnestic and clinical evaluation**.** A clinical response to an elimination diet is a diagnostic indicator. In addition, results from food allergy (FA) screening tests, which include skin-prick tests (SPT) and the determination of serum level of specific IgE against CMP, can determine CMA in an infant**.**[1,2] Atopy patch tests can predict oral tolerance in children with gastrointestinal symptoms related to nonimmunoglobulin E-mediated CMA, and determines whether an oral food challenge can be undertaken safely.[3,4] Results of a diagnostic oral food challenge (OFC)—one of the most traditional means of testing—can also determine CMA**.** In selected patients, gastrointestinal tests are used, such as an endoscopy with multiple biopsies and/or other invasive or noninvasive tests to confirm the allergic nature of the disease.

Treatment for Children with Cow's Milk Allergy

It is common to treat a food allergy through an elimination diet, avoiding CMP in any form. Specific to cow's milk allergies is that special formulas can be used to treat these patients, including extensively hydrolyzed whey or casein formula, or soy formula, as a first-line choice.[2,5] In addition, amino acid-based formula (AAF) is used in children who are intolerant to the abovementioned special formulas.

The most recent European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) clinical guidelines recommend initial administration of an extensively hydrolyzed CMP formula in most infants with CMA, noting that it is well tolerated and less expensive.[6]

Oral Food Challenge

To determine whether oral tolerance has been achieved, the only strategy that can be adopted in clinical practice is the oral food challenge (OFC), which exposes the child to increasing doses of cow's milk and then assesses the clinical response. In general, an OFC assesses the possible occurrence of oral tolerance after at least 6 months or at least 12 months of an exclusion diet in non-IgE mediated and IgE-mediated patients, respectively. Clinical data suggest that a strong reaction from an SPT could be predictive of a positive OFC, thus it is prudent to perform an SPT before the challenge.[7]

Differences Between Partially and Extensively Hydrolyzed Formula

Specific formula types influence the acquisition rate of tolerance in children with CMA. The main difference derives from the degree of the hydrolysis. The American Academy of Pediatrics defines extensively hydrolyzed formula as containing only amino acids or small peptides with a molecular weight less than 3,000 kilodalton (kDa), whereas partially hydrolyzed formulas are those containing peptides with a molecular weight greater than 5,000 kDa.[8] Partially hydrolyzed formula could be considered for CMA prevention in babies aged less than 4 to 5 months who cannot be exclusively breastfed.[8]

Role of Probiotic LGG

Lactobacillus rhamnosus strain GG (LGG) is the most studied probiotic in the pediatric field, particularly for food allergy. LGG**,** when used alone or in combination with extensively hydrolysed casein formula (EHCF), plays a significant role when administered during infancy to prevent or treat CMA. Numerous studies have demonstrated a strong immunoregulatory anti-inflammatory and anti-allergic effect elicited from this probiotic. Trial data (Canani et al, 2016) show EHCF added to LGG counteracts allergy pathways, modulating the interaction among dietary agents, gut microbiota, epigenetic mechanisms, and the immune system.[5,7] Clinical trials have demonstrated that the use of LGG during pregnancy, and in the first weeks of life, could be helpful in preventing eczema and other atopic manifestations.[1] It has been

demonstrated that EHCF supplemented with LGG in infant formula is able to induce a faster resolution of gut inflammation in children affected by CMA.[1,9]

Mechanism of Action of LGG added to EHCF

The mechanisms of action elicited by LGG are multiple. These include positive effects on gut microbiota dysbiosis; short-chain fatty acid production; modulation on nonimmune protective factors, including intestinal permeability and mucus production; and epigenetic regulation of Th1 and Th2 cytokine genes expression.[10]

Clinical Benefits Proposed from Clinical Trials

Data suggest that there is a faster acquisition of oral tolerance with the use of EHCF and added LGG in children affected by IgE or non-IgE-mediated CMA, compared to other dietary strategies such as AAF, soy or rice formula, or standard EHCF.[5] This is a result of the positive modulation of gut microbiota composition that increases the number of good bugs—markers of a healthy microbiota—that are able to produce a large amount of the short-chain fatty acid, butyrate. Additional benefits include faster and stronger epigenetic modulation on Th1 and Th2 cytokine genes expression. The dietary intervention with EHCF supplemented with LGG has also been show to influence the occurrence of other allergies in children with IgE-mediated CMA.[7]

Long-Term Implications of Cow's Milk Allergy

CMA patients, particularly the persistent cases with IgE-mediated mechanism, develop substantial predisposition to other allergic diseases, such as asthma, urticaria, oculorhinitis, which is a phenomenon of symptom progression labeled atopic march. A study from the US Centers for Disease Control and Prevention shows that children with food allergies are 2 to 4 times more likely to have other allergies, such as asthma (4.0 times), atopic eczema (2.4 times), and respiratory allergies (3.6 times), compared with children without food allergies.[7]

Discussion Guide

- What are common causes and symptoms of cow's milk allergy?
- What are the long-term implications of CMA, if left untreated?
- How do you differentiate special formulas that can be used to treat patients with CMA?
- What are the clinical benefits of the probiotic LGG when added to EHCF, according to recent clinical trial data?
- Should this information prompt a change in current clinical practice?

Suggested Readings and Resources

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