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In this issue:

What Every Canadian Physician Should Know About Cow's Milk Protein Allergy

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Cow's milk protein allergy is one of the most common food allergies, affecting an estimated 1 in 40 Canadian infants (Høst, 2002), but its variety of presentations make it notoriously tricky to diagnose (Boné 2009, Luyt 2014). This short primer, written in response to results from a national needs assessment, offers a clear guide to symptoms and a step-by-step pathway to diagnosis. A promising line of research into accelerating oral tolerance is also discussed.

COW'S MILK PROTEIN ALLERGY: A BURDENSOME CONDITION

> **Learning Point:** IgE-mediated and non-IgE-mediated cow's milk protein allergies present differently and require different management approaches.

DESCRIPTION

Cow's milk protein allergy (CMPA) is a condition in which the immune system mounts an immune-based reaction against the proteins in cow's milk, which include caseins and whey proteins. Reactions are classified as either immunoglobulin E (IgE)-mediated or non-IgE-mediated, and the two types of reaction can occur together. The vast majority of infants with CMPA eventually outgrow it (Motala, 2012).

CMPA is different from lactose intolerance, a condition that rarely develops before the age of 3 years in which the affected individual cannot properly digest lactose (sugar); congenital lactose malabsorption is extremely rare. Lactose intolerance usually develops during childhood as the capacity to digest lactose decreases. CMPA is also different from infantile colic, a condition that presents as unexplained intense but benign crying in a newborn, typically lasts 3-8 weeks, then gradually diminishes and eventually disappears. (CPS handout)

PRESENTATION

CMPA typically presents in the first weeks or months of life. Onset after the age of 12 months is rare (Luyt, 2014). The way in which infants present depends on whether their CMPA is IgE-mediated, non-IgE-mediated, or a combination of the two types.

IgE-mediated reactions are acute, tend to develop rapidly after consumption of cow's milk protein (CMP), and are diverse in their symptoms. Because they are mediated by IgE antibodies, which demands a certain immune maturity, they usually only manifest after the first few months of life.

Non-IgE-mediated Although commonly included under the umbrella term "CMPA," non-IgE-mediated responses are more accurately defined as food-protein-induced enteropathies or food-protein-induced intolerances. This condition develops earlier in life (as early as the first few days or weeks) and has a more insidious spectrum of manifestations, including growth failure and gastrointestinal symptoms of various levels of severity (for example, enterocolitis, proctocolitis, and food-protein-induced enterocolitis syndrome [FPIES]; see Table 1).

Table 1. Presentation of IgE- and non-IgE-mediated CMPA.

	IgE-mediated CMPA	Combined CMPA	Non-IgE-mediated (e.g., enterocolitis; proctocolitis; FPIES) CMPA
Reaction Type	Acute	Variable	Non-acute
Rapidity of Symptom Development	Minutes to hours	Variable	Several hours to several days
Typical Age of Presentation	After several months of life	Variable	After a few days or weeks of life
GI Symptoms	• Abdominal pain • Vomiting • Diarrhea	Variable	• Esophagitis • Gastritis • Enteritis • Enterocolitis • Proctocolitis
			Upper GI: • Vomiting (if repetitive can lead to hypotension*) • Severe reflux • Irritability
			Middle GI: • Abdominal cramping • Abnormal bowel movements • Failure to thrive
			Lower GI: • Mucus and/or blood in stools
Skin-related Symptoms	• Urticaria • Redness • Angio-œdema • Pruritus		--
Respiratory Symptoms	• Cough • Wheezing • Acute rhino-conjunctivitis • Respiratory distress/Dyspnea		--
Systemic Symptoms	• Hypotension • Lethargy		--
Possible Disorders	Anaphylaxis	• Atopic Dermatitis • Food-protein-induced enterocolitis syndrome (FPIES) • Eosinophilic esophagitis	--

* Mainly in food protein-induced enterocolitis syndrome

Table developed by Dr. Marie-Josée Francœur, Dr. Reza Alizadehfar, Dr. Valérie Marchand and Dr. Saul Greenberg, 2016. Adapted from Boné J, *et al. Allergol Immunopathol (Madr)*. 2009:37:36-42.

CLINICAL MANIFESTATIONS OF COW'S MILK PROTEIN ALLERGY

Learning Point: Onset of symptoms is a useful way to categorize IgE-mediated and non-IgE-mediated CMPA (Motala Fiocchi, 2012)

IMMEDIATE REACTIONS

IgE-mediated: These typically occur less than two hours after ingestion; the most common are cutaneous (urticarial, angioedema, acute flare-up of atopic eczema) and gastrointestinal (vomiting, diarrhea, discomfort).

DELAYED REACTIONS

Non-IgE-mediated: These appear several hours to several days after consumption of CMP. The most common GI disorders are food-protein-induced (FPI) enterocolitis, enteropathy, and proctocolitis. Milk-induced proctocolitis presents more frequently in young infants who are exclusively breast-fed than in those fed formula. Food-protein-induced symptoms include diarrhea, mucus in the stool, rectal bleeding, vomiting, gastroesophageal reflux, discomfort and poor growth. Some children may present with isolated hypoalbuminemia and iron deficiency anemia.

For a complete presentation of IgE- and non-IgE-mediated CMPA symptoms, please refer to the preceding chart.

DIAGNOSING COW'S MILK PROTEIN ALLERGY

Learning Point: The first step in diagnosing cow's milk protein allergy is obtaining a detailed description of the nature, severity, and onset of symptoms.

THE STARTING POINT: A DETAILED PATIENT HISTORY

As described in Table 1, IgE- and non-IgE-mediated CMPA present differently. When taking a patient history, caregivers should be asked about the infant's specific symptoms, their severity, and the timing of their appearance. On the basis of this description, conditions with similar presentations (e.g., gastroesophageal reflux, lactose intolerance, colic) can usually be ruled out. Often, the detailed description will point to either an IgE-mediated or alternatively a non-IgE-mediated CMPA. For example, the appearance of several acute symptoms (e.g., vomiting, wheezing and angio-oedema) shortly after consumption of cow's milk protein should raise red flags for IgE-mediated CMPA, and the symptom of diarrhea containing blood and mucus in an otherwise healthy infant should raise particular suspicion for non-IgE-mediated CMPA (Luyt 2014). In most cases, though, further information will be required.

FOR SUSPECTED IGE-MEDIATED CMPA: SKIN PRICK TESTING, ANTIBODY TESTING, AND FOOD CHALLENGES

In the case of suspected IgE-mediated allergy, it is recommended that the infant be referred to an allergist who will perform the appropriate investigations.

A diagnosis of IgE-mediated disease can generally be confirmed or ruled out through a detailed history, sometimes combined with skin prick testing or serum-based measurement of IgE antibodies (Luyt 2014, Brill 2008, Motala Fiocchi 2012). Following an elimination diet, open food challenges under medical supervision can also confirm reactions to cow's milk; if symptoms are atypical or subjective, a blinded challenge may be necessary (Luyt, 2014).

FOR SUSPECTED NON-IGE-MEDIATED CMPA: DIETARY ELIMINATION AND RE-CHALLENGE

The standard approach when non-IgE-mediated CMPA is suspected is to eliminate cow's milk protein from the infant's diet for 2-3 weeks, observe if symptoms resolve, then test whether reintroduction of cow's milk protein provokes a reaction (Brill 2008, Motala Fiocchi 2012, Vandenplas 2007). In order to achieve elimination, breastfeeding mothers must avoid all

cow's milk proteins and those derived from goat's and sheep's milk, and ensure any infant formula they use is hypoallergenic (e.g., extensively hydrolysed formula). In selected cases a rectoscopy with rectal biopsies may be warranted. The finding of an eosinophilic infiltrate on rectal biopsy confirms the diagnosis.

IF DOUBT REMAINS, CONSULT WITH A COLLEAGUE

Because of its diverse presentation, accurately diagnosing CMPA can be a challenge even for experienced physicians. Consultation with a colleague may shed light on a complex patient case. (Opinion of the Expert Committee Members)

CURRENT MANAGEMENT APPROACH: AVOIDANCE OF COW'S MILK PROTEIN

Learning Point: The first objective of CMPA management is resolution of the immune-based reaction and inflammation. The second is the development of oral tolerance.

FIRST OBJECTIVE: RESOLVE SYMPTOMS

The first objective in the management of CMPA is to resolve the immune based reaction and inflammation from which the symptoms derive. This involves elimination of cow's milk protein from the infant's diet. It is important that a nutritionist be part of the patient care team to provide the family with guidance regarding avoidance of milk and the maintenance of adequate nutritional intake, especially of calcium and Vitamin D.

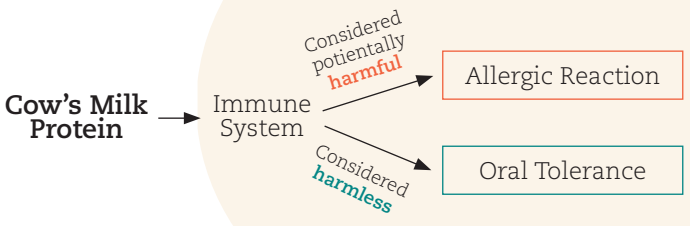
If mothers are breastfeeding, they must avoid all cow's milk, goat's milk and sheep's milk dairy products.** If infant formula is being used, it must be hypoallergenic (see Table 2). If the infant has reached the age where he or she can eat solid foods, cow's milk proteins must be avoided.

This kind of elimination diet is highly burdensome for the family. As the child ages, if the allergy has not yet resolved, the burden extends outside of the family. Special accommodations must be made by the daycare or school, and the child's dietary restrictions must be taken into account at social events to which the child is invited (e.g., other children's birthday parties). An epinephrine autoinjector should always be on hand due to the risk of IgE-mediated anaphylaxis.

SECOND OBJECTIVE: ENCOURAGE THE DEVELOPMENT OF ORAL TOLERANCE

When a newborn infant's gut is inundated with foreign proteins, the gastrointestinal immune system—one of the body's first lines of defense against ingested material—must make an important determination: Is the foreign material potentially harmful, in which case an immune response should be mounted? Or is it harmless, in which case subsequent immune reactions should be suppressed? The immune system's decision to suppress future reactions to harmless antigens, like cow's milk protein, is referred to as the development of oral tolerance (see Figure 1) (Pabst Mowat 2012, Nermes 2013).

Figure 1. Oral tolerance is achieved when the immune system recognizes that cow's milk protein is innocuous and fails to mount a defense against it.



Adapted from: Pabst Mowat 2012; Nermes 2013

It remains unclear how best to encourage the development of oral tolerance. Some hypotheses currently under investigation, such as the possibility of "teaching" the immune system to develop oral tolerance for IgE-mediated allergies through low-dose exposure to cow's milk protein (known as oral immunotherapy), are described in the "New Directions" section on the next page.

It is worth noting in relation to both food challenge testing (in which CMP is introduced gradually following an elimination diet) and oral tolerance induction, described on the following page, that the severity of a previous reaction does not predict the severity of a future reaction, with previous mild reactions being followed by anaphylactic responses in some cases. (Vandenplas 2007, Motala Fiocchi 2012)

Table 2. Which Formulas Are Acceptable for Infants with CMPA? (Fiocchi 2010, AAP 2000, Vandenplas 2007, Motala Fiocchi 2012, Koletzko 2012, Opinion of the Expert Committee)

IgE-Mediated CMPA		Non-IgE-Mediated CMPA
This is the formula of choice	**Extensively hydrolyzed formulas.** These are formulas in which the proteins (for example, casein) have been broken down (hydrolyzed) into tiny fragments.	This is the formula of choice
	Partially hydrolyzed formulas. These formulas, in which the proteins have only been partially hydrolyzed, contain residual allergens.	At diagnosis:  At 12 months:  This formula can become useful at around 12 months as a transition formula before the reintroduction of cow's milk
In rare cases where optimal response to extensively hydrolyzed formula is not achieved, these formulas are a second-line choice.	**Amino acid-based formulas.** These contain no protein at all, just amino acids.	In rare cases where response to extensively hydrolyzed formula is not achieved after 2 weeks, these formulas are a second-line choice.
These are not appropriate for infants with allergy	**Lactose-free formulas.** These are formulas that contain cow's milk protein but no lactose.	These are not appropriate for infants with allergy
If the infant has no soy allergy, soy preparations can be used at around 9 months of age or slightly earlier. They are especially useful if the taste of extensively hydrolysed formula becomes a challenge.	**Soy-based formulas.**	Some infants with non-IgE-mediated CMPA may have the same GI symptom reactions to soy. Soy can be used as an alternative to dairy in breastfeeding mothers.

** Importantly, cessation of breastfeeding is not warranted in all cases. If an infant diagnosed with IgE-mediated CMPA following an acute reaction is currently being breastfed without any symptoms by a mother who is consuming dairy products, breastfeeding should continue in the hopes of encouraging oral tolerance in the infant.

NEW RESEARCH: ACCELERATING ORAL TOLERANCE TO COW'S MILK PROTEINS

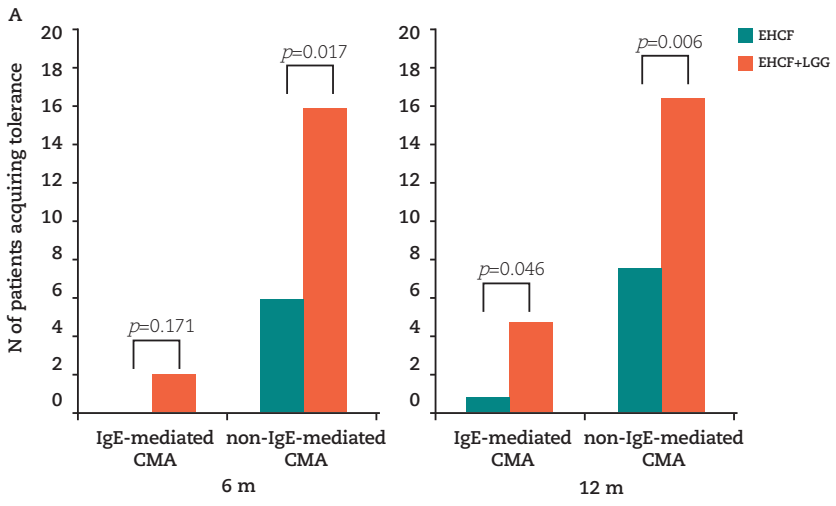
Novel areas of research: Oral immunotherapy and supplementation of extensively hydrolyzed formula with the probiotic *Lactobacillus rhamnosus* GG

With the impressive results of the LEAP study showing a significant decrease in the development of peanut allergy in at-risk infants thanks to early introduction of peanuts into the diet (Du Toit 2015), there has been increased focus on accelerating the acquisition of oral tolerance to CMPA.

Multiple studies have investigated the effectiveness and safety of inducing oral tolerance by deliberately administering cow's milk, starting with doses too low to provoke a reaction and increasing gradually to either a target dose or to the highest tolerable dose (Burbank 2016, Staden 2007, Martorell 2007, Brozek 2012, Longo 2012). This approach, known as immunotherapy, is still considered investigational but it shows promise, especially for children in whom the allergy persists beyond the first few years of life. (Luyt, 2014)

Another intervention that has been explored in two small, hypothesis-generating Italian studies is dietary supplementation with the probiotic *Lactobacillus rhamnosus* GG (LGG)(Berni Canani JACI 2012; Berni Canani, J Pediatr, 2013). In these studies, both of which lasted a full year, infants aged 1-12 months were fed an exclusive diet of either extensively-hydrolyzed casein formula (EHCF) enriched with LGG (concentration: ≥1.4 x 10^7 colony-forming units/100 mL) or another formula (EHCF in the first study, or one of four other formulas including EHCF in the second study). At all time points (6 and 12 months in the first study, and 12 months in the second study), the rate of acquisition of oral tolerance was significantly higher in infants fed LGG-enriched EHCF vs. any other formula (see Figure 2).

Figure 2: In the first of two studies by Berni Canani *et al.*, significantly more infants receiving LGG-enriched EHCF vs. regular EHCF acquired oral tolerance at 6 and 12 months



Both studies were small and had methodological limitations. Most important was the fact that patients who had experienced anaphylaxis, and therefore had confirmed IgE-mediated CMPA, were excluded from both studies. Also, the fact that fresh cow's milk rather than the standard allergen extracts was used for skin prick tests and atopic patch tests (which is a less reliable way of confirming CMPA) is problematic.

Although LGG-enriched EHCF has been available to consumers in Europe for over a decade and was recently introduced in the United States, as of the time of printing it is not available on the Canadian market. Even if it were, large, robustly-designed, long-term studies in a North-American population would have to be conducted before its applicability to clinical practice in Canada could be evaluated. Such research could also clarify how long infants in each population (those with IgE-mediated vs. non-IgE-mediated reactions) need to be fed LGG-EHCF, and at what concentration and frequency, before they can be re-challenged. Nonetheless, this line of research seems promising.

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