Lactose Intolerance in Pediatric Patients and Common Misunderstandings About Cow's Milk Allergy

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ABSTRACT

Lactose intolerance is a common gastrointestinal condition caused by the inability to digest and absorb dietary lactose. Primary lactose intolerance is the most common type of lactose intolerance. It is one of the most common forms of food intolerance and occurs when lactase activity is reduced in the brush border of the small bowel mucosa. People may be lactose intolerant to varying degrees, depending on the severity of these symptoms. When lactose is not digested, it is fermented by gut microbiota, leading to abdominal pain, bloating, flatulence, and diarrhea with a considerable intraindividual and interindividual variability in the severity of clinical manifestations. These gastrointestinal symptoms are similar to cow's milk allergy and could be wrongly labeled as symptoms of "milk allergy." There are important differences between lactose intolerance and cow's milk allergy. Therefore, a better knowledge of these differences could limit misunderstandings in the diagnostic approach and in the management of these conditions. **[*Pediatr Ann*. 2021;50(4):e178-e185.]**

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Adverse food reactions (AFRs) in children can derive from several mechanisms triggered by different components of the same food.[1] Immune-mediated reactions (eg, food allergy, celiac disease) are elicited by food proteins, whereas non–immune-mediated AFRs usually derive from carbohydrate intolerances. Lactose intolerance is the most common carbohydrate intolerance in childhood. Lactose is the main carbohydrate in human breast milk and cow's milk; it is also present in many dairy products. It is a disaccharide composed of galactose linked to glucose, and it requires hydrolysis by beta-galactosidase (lactase) bound to the small intestine brush border membrane before it can be absorbed. Lactose intolerance primarily refers to a syndrome having one or more intestinal or extra-intestinal symptoms upon the consumption of foods containing lactose that derives from insufficient level of lactase activity in the brush border of the small bowel mucosa.[2]

This article aims to provide an overview of the clinical classifications, presentation, and management of lactose intolerance in pediatric patients, highlighting several common misunderstandings with cow's milk allergy (CMA) to avoid common pitfalls in treatment and management.

CLINICAL CLASSIFICATIONS OF LACTOSE INTOLERANCE

There are four main clinical types of lactose intolerance: (1) developmental lactase deficiency, (2) congenital lactase deficiency, (3) primary lactose intolerance, and (4) secondary lactase deficiency.

Developmental Lactase Deficiency

Developmental lactase deficiency is observed in infants born prematurely (26-34 weeks of gestation) and is caused by temporary lactase deficiency that improves with time. Lactase is the last of the small intestinal disaccharides to develop during intrauterine development. The peak lactase expression is reached at term, when an infant typically tolerates up to 60 to 70 g of lactose per day (approximately 1 L of breast milk).[3]

Congenital Lactase Deficiency

Congenital lactase deficiency (CLD) is a rare (only a few cases have been described) and severe intestinal autosomal recessive disease (within the group of congenital diarrheal disorders [CDD]), caused by the absence of lactase activity from birth.[4,5] During the first days after birth, with the onset of consuming breast milk or lactose-containing formula, the newborn presents with watery diarrhea, intestinal meteorism, and failure to thrive. All symptoms disappear when patients change to a lactose-free diet. The typical feature of CLD is the absence or low levels of lactase expression deriving from a mutation in the lactase phlorizin hydrolase gene (*LPH*) located on 2q21.3.[6] Most CLD cases have been described in Finland, where the disorder is more common due to a founder effect and genetic drift.[7] Premature stop codons and a truncated protein because of frame shifts, missense mutations in the coding region of *LPH*, or exon duplication are the most common genotypes identified in these patients.[7-10] Some other cases include mutations leading to single amino acid substitutions that can interfere with the proper maturation and function of *LPH*.[7,11] More recently, severe forms of CLD elicited by mutations in the *LPH* gene that occur in either a compound heterozygous or homozygous pattern of inheritance have been described.[4]

Primary Lactose Intolerance or Adult-Type Lactase Deficiency

Primary lactose intolerance, also called hypolactasia or lactase non-persistence, is the most common type of lactose intolerance and is genetically determined. It is due to a gradual decline of intestinal lactase expression and activity, making dairy products difficult to digest later in childhood or adolescence. This occurs in about 70% of the global adult population. The global distribution and the age at which lactase expression declines vary with ethnicity. It is most common in African Americans, Hispanics/Latinx, and Asians, and is least prevalent in people of European descent. People who develop primary lactose intolerance start life producing lactase, and during infancy lactose accounts for most of their dietary carbohydrates. As children grow older and replace milk with other foods their lactase production decreases. Children of African, Asian, or Hispanic/Latinx descent may experience symptoms beginning between ages 2 and 3 years, whereas children of European descent typically do not develop symptoms of lactose intolerance until later in childhood (age 5-6 years) or adolescence.[12-14] Several individual variables can influence the development of symptoms in people with non-persistence, such as dose of lactose in diet, intestinal transit time, lactase expression, distribution and fermentation ability of gut microbiota, sensitivity toward chemical and mechanical stimulation of the gut, and psychological factors.[15,16]

Secondary Lactose Intolerance

Secondary lactose intolerance occurs because of small bowel damage that causes a reduction in lactase expression, determining a secondary and transient lactase deficiency. Among the diseases associated with secondary lactose intolerance are celiac disease, small intestine bacterial overgrowth, and Crohn's disease. Treatment of the underlying disorder may restore lactase levels and improve signs and symptoms, although it can take time. Abdomen radiation therapy or chemotherapy could also lead to lactose intolerance.[17] CMA can cause severe enteropathy with secondary lactase deficiency. In these patients, there may be an overlap of gastrointestinal symptoms due to CMA and lactose intolerance.[18] Few studies reported the prevalence of secondary lactose intolerance in children age 1 to 5 years. The range of prevalence of secondary lactose intolerance is between 0% and 19%, with no obvious regional differences. The studies state diverse causes for secondary lactose intolerance, ranging from infectious diarrhea to CMA.[19]

DIFFERENT MECHANISMS BETWEEN LACTOSE INTOLERANCE AND COW'S MILK ALLERGY

Frequently, among both patients and physicians, there is confusion about the difference between lactose intolerance and CMA, which could result in unnecessary dietary restriction or avoidable reactions. "Milk allergy," "milk intolerance," and "lactose intolerance" are often used by patients and their parents without a clear sense of the different meanings, understanding of the differ-

ent mechanisms that underlie them, or the dietary implications of the diagnosis. The management of these conditions is distinctly different, and inappropriate recognition or management may have significant implications for the patient.[18,20] The same food, cow's milk, can lead to an adverse reaction through different mechanisms.

Lactose intolerance results from a reduced ability to digest lactose, a sugar. As explained above, lactose intolerance is a non–immune-mediated AFR, whereas CMA is one of the most common forms of food allergy (an immune-mediated AFR), particularly in the the first years of life. Cow's milk allergy may be due to immunoglobulin E (IgE)-mediated, non–IgE-mediated, or mixed reactions.[21] Children with CMA have an allergic reaction to cow's milk proteins but they are able to tolerate lactose, whereas children with lactose intolerance have a reduced ability to digest lactose but they tolerate cow's milk protein. Because of these different pathogenetic mechanisms, a small amount of cow's milk proteins could cause an allergic reaction. In contrast, many people with lactose intolerance can often tolerate small amounts of lactose and can tolerate cow's milk protein fully. CMA can cause severe enteropathy with secondary lactase deficiency. In these patients, there may be an overlap of gastrointestinal symptoms due to CMA and lactose intolerance.

THE CLINICAL SYMPTOMS OF LACTOSE INTOLERANCE AND CMA IN CHILDREN

Nondigested lactose in the intestinal tract drives fluids into the gut lumen through an osmotic force, causing osmotic diarrhea. Moreover, gut microbiota ferment lactose, producing volatile fatty acids and gases (hydrogen, methane, and carbon dioxide). All these events are responsible for the clinical symptoms, such as distension of the small bowel, nonfocal abdominal pain associated with bloating and flatulence, nausea, increased gut motility, and diarrhea.[22] These symptoms usually develop from 30 minutes to 2 hours after the ingestion of lactose-containing foods. Food intolerances have long been reported by patients with functional gastrointestinal disorders; however, randomized controlled trials are lacking in this area.[23] Extra-intestinal symptoms, such as headache, vertigo, memory impairment, and lethargy have been described in up to 20% of people with carbohydrate intolerance.[24] These systemic symptoms could be the result of toxic metabolites, produced by fermentation of sugar by colonic bacteria that can alter cell-signaling mechanisms.[25] However, it is unclear whether these atypical symptoms are directly due to lactose ingestion or related to the presence of the "functional disease," which is frequently accompanied by multiple somatic complaints.

In children with CMA, the clinical presentation is different among IgE-mediated reactions, non–IgE mediated reactions, and mixed reactions. After food intake, IgE-mediated reactions typically occur within 2 hours, whereas non–IgE mediated reactions develop 2 to 48 hours (or even later) after the ingestion of the food.[21] In particular, lactose intolerance can cause a great deal of discomfort, but it will not produce a life-threatening reaction such as anaphylaxis. The gastrointestinal symptoms of non–IgE-mediated CMA are frequently wrongly labeled as symptoms of intolerance. The typical non–IgE-mediated presenting symptoms are usually gastrointestinal in origin and lead to crying and irritable infants, colic, gastroesophageal reflux, abdominal pain, vomiting, and diarrhea. Eczema is another frequent presenting symptom. In addition, these symptoms are commonly reported in infants with no underlying CMA.[18] As a result, symptoms are often not linked to this disorder, leading to underdiagnosis, incorrect diagnosis, and/or delayed diagnosis. The main differences between CMA and lactose intolerance are summarized in the **Table 1**.

DIAGNOSTIC APPROACH TO A CHILD WITH SUSPECTED LACTOSE INTOLERANCE AND DIFFERENTIAL DIAGNOSIS WITH CMA

The mainstays of adult-type lactose intolerance diagnosis are anamnesis and lactose breath test (LBT).[26] The LBT is a rapid, noninvasive test that allows measuring the content of hydrogen in the expired air. The dose of lactose administered is 1 g/kg in children. Although high doses of lactose (≥50 g) have been used for LBT, 25 g (equivalent of 500 mL of milk) is within the normal range of consumption and is the recommended dose after 8 to 12 hours of fasting.[27] All breath testing should incorporate measurement of CO_2 (or O_2) to adjust the breath sample for non-alveolar dilution of exhaled air.[28] Concomitant measurement of CH_4 is also required because detection rate of an early rise in H2 production significantly decreases in people who produce excess methane.[27] A cut-off increase of H2 of 20 parts per million (ppm) above the baseline level is considered as positive (CH_4 ≥10 ppm).

Factors that may produce false-negative or false-positive results include conditions affecting the gut microbiota (eg, recent use of antibiotics), lack of hydrogen-producing bacteria (10%-15% of the population), ingestion of high-fiber diets before the test, small intestinal bacterial overgrowth, or intestinal motility disorders.[26,29]

A diagnostic test that was popular in the past was the lactose tolerance test; however, because of the high rate of

false-negative and false positive-results, this test should not be used and has been replaced by the LBT.[30,31]

Another diagnostic test available is the genetic test, which identifies single nucleotide polymorphisms associated with lactase persistence/non-persistence. It should be emphasized that the presence of the lactase non-persistent gene does not imply the simultaneous presence of lactose intolerance that may appear later in life. Genetic testing for mutations of the *LPH* gene should be performed whenever CLD is suspected in infants with typical symptoms and a positive response to dietary elimination of lactose.

In secondary lactase deficiency, a good clinical history often reveals the relationship between lactose ingestion and symptoms. The differential diagnosis between CMA and primary/secondary lactose intolerance is based on an allergy-focused clinical history. A personal and family history of atopic disease (such as asthma, eczema, or allergic rhinitis) or food allergy is more likely in CMA. An assessment of presenting symptoms and other symptoms that may be associated with CMA could be useful, including questions about age at symptom onset, speed of onset, duration of symptoms, severity of reaction, frequency of occurrence, setting of reaction, and reproducibility of symptoms. It is also relevant to focus on the weaning age, the type of feeding, details of any previous treatment and the response to it, any response to the elimination, and reintroduction of foods. If an IgE-mediated reaction is suspected, it can be useful to perform an allergy screening with skin prick test or blood test. For non–IgE-mediated reactions, the suspected allergen (eg, cow's milk protein) must be removed from the diet for a period of 2 to 6 weeks to see if the symptoms go away, and then it is put back in to see if the symptoms come back. This oral food challenge gives the diagnosis of delayed CMA.[20]

TABLE 1.

Main Differences Between Primary Lactose Intolerance (Lactase Non-Persistence) and Cow's Milk Allergy

Criterion	Lactose intolerance	Cow's milk allergy
Mechanism	Enzyme deficiency	Immune-mediated reaction
Onset of symptoms	Age 5-6 years	Peaks during the first year of life
Resolution	Irreversible	Tends to resolve in childhood (age 2-5 years)
Food component involved	Lactose	Cow's milk proteins
Eliciting doses	Grams	From nanograms to milligrams
Gastrointestinal symptoms	Abdominal pain, nausea, bloating, flatulence, and diarrhea (less common: constipation, vomiting)	IgE-mediated urticaria; angioedema of the lips, tongue, and palate; oral pruritus; nausea; colicky abdominal pain; vomiting; diarrhea Non–IgE-mediated: vomiting, diarrhea, blood and/or mucus in the stools, abdominal pain, malabsorption often associated with failure to thrive or poor weight gain
Extra-intestinal symptoms	Headache, vertigo, memory impairment, and lethargy	IgE-mediated: skin (acute urticaria and/or angioedema); respiratory system (nasal itching, sneezing, rhinorrhea, or congestion, and/or conjunctivitis, cough, chest tightness, wheezing, or shortness of breath); other (signs or symptoms of anaphylaxis) Non–IgE/IgE-mediated: atopic eczema
Test to confirm the diagnosis	Lactose breath test	Oral food challenge
Dietary treatment	Low-lactose diet	Cow's milk proteins-free diet

Abbreviation: IgE, immunoglobulin E.
Adapted from Di Costanzo and Berni Canani.[48]

THE DIFFERENT MANAGEMENT OF LACTOSE INTOLERANCE AND CMA

The mainstay of treatment for AFRs is to remove the causative food from the diet. In AFRs induced by CMA, small protein doses can cause symptoms, so the management is based on the strict avoidance of the cow's milk-derived allergenic peptides from the diet. On the contrary, reduction of lactose intake rather than full exclusion is recommended in lactose intolerance, because available data suggest that adolescents and adults can usually ingest up to 12 g of lactose in a single dose (equivalent to 1 cup or 240 mL of milk) with no or minimal symptoms.[32] So, in these patients, dietary treatment consists only in a low-lactose diet (**Table 2**).[2,32]

TABLE 2.

Low-Lactose Diet

- Foods to limit
  - All dairy milk (whole, low fat, nonfat, cream, powdered, condensed, evaporated, goat, acidophilus, and flavored [chocolate, strawberry])
  - Butter
  - Cottage cheese
  - Ice cream
  - Creamy/cheesy sauces
  - Cream cheeses
  - Soft cheeses (brie, ricotta, mozzarella)
  - Whipped cream
  - Yogurt
  - Fish and meat that is breaded or creamed
  - Milk bread, crackers
  - Creamed, scalloped, or au gratin potatoes
  - Muffins, biscuits, waffles, pancakes, and cake mixes
  - Bakery products and desserts that contain the ingredients listed above
  - Milk chocolate
- Foods allowed
  - Lactose-free milk (lactaid, soy, almond, oat milk)
  - Lactose-free dairy, hard cheeses (Parmigiano Reggiano, Pecorino, Grana Padano, fontina, taleggio, provolone, Swiss), gorgonzola
  - All fruits
  - All vegetables
  - All legumes
  - All cereals
  - All meat, fish, and eggs
  - All vegetable fats

Adapted from Di Costanzo and Berni Canani.[48]

There is no scientific evidence to identify the tolerable dose of lactose for children with lactose intolerance. Determining the amounts of lactose that can be tolerated is necessary to develop evidence-based dietary recommendations that meet the needs of the person. In primary lactose intolerance, lactose-containing dairy products are generally avoided for 2 to 4 weeks, which is the amount of time required to induce symptom remission. Then, a gradual reintroduction of dairy products low in lactose up to a threshold dose of individual tolerance should be recommended.

In secondary hypolactasia, a restricted diet is necessary only for a limited time.[32] Concern about lactose intolerance and osmotic diarrhea in the treatment of undernourished children has led to restricted use of lactose in these patients. Even in well-nourished children, low-lactose formulas are frequently used in children with persistent diarrhea. It is useful to find a balance in which the amount of lactose in food does not induce osmotic diarrhea but allows beneficial effects of lactose. Clinical trials are needed to better define the safe and appropriate lactose dietary levels for moderately and severely undernourished children.[33] In the rare case of CLD, a complete lactose-free diet is required for the remainder of the patient's life.

Enzyme replacement and probiotics are other therapeutic approaches in patients with lactose intolerance who wish to enjoy dairy products.[34-39] Further studies are required to provide high-quality evidence to support or compare the efficacy of all these strategies.

NUTRITIONAL ISSUES ASSOCIATED WITH A LOW OR LACTOSE-FREE DIET

Lactose-free diets are currently in fashion. In supermarkets, dozens of products labeled as lactose-free can be easily found, and cafes, ice-cream shops, bakeries, and restaurants offer special menus with foods that contain no lactose. Milk consumption is decreasing in the United States and is the lowest in countries with a high prevalence of lactase non-persistence.[14] Preliminary evidence shows that elimination of lactose from an infant's diet is disadvantageous for the development of healthy gut microbiota,[40] and there is a different plasma metabolic profile in children fed a lactose-free formula.[41] A lactose-free diet should be prescribed only when a true diagnosis of lactose tolerance is achieved. Full exclusion of dairy from the diet may affect other health outcomes. It is important to understand that if dairy products are eliminated, other dietary sources of calcium or calcium supplements need to be provided. The current recommendations for calcium intake are 700 mg/day for children age 4 to 9 years, and 1,300 mg/day for children age 10 years and older according to the European Food Safety Authority guidelines.[42] Good sources of calcium in a low- or lactose-free diet are dark-green leafy vegetables such as spinach, broccoli, and kale, nuts (almonds), beans (white beans), fish (sardines, salmon), and calcium-fortified orange juice. If these foods are not enough, a calcium supplement must be considered.

Educational and commercial efforts to improve calcium and vitamin D intake are now focusing on stimulating the consumption of tolerable amounts of milk and the use of low lactose-containing foods including hard cheeses, yogurt, and lactose-hydrolyzed milk products.

INAPPROPRIATE PRESCRIPTION OF LACTOSE-FREE OR LACTOSE-REDUCED FORMULA IN INFANTS WITH CMA

A survey conducted in Northern Ireland from 2012 to 2014 assessed formula prescription patterns in infants with likely non–IgE-mediated CMA.[43] The survey found that thickened anti-regurgitation formula, lactose-

reduced partially hydrolyzed formula or lactose-free formula, and cow's milk protein-containing formulas were commonly prescribed in infants with symptoms suggestive of non–IgE-mediated CMA.[43] The survey was repeated after the implementation of active education and national feeding guidelines.[43] After the educational interventions, there was a significant increase in prescription of hypoallergenic formulas (including amino acid-based formula and extensively hydrolyzed formulas) and a decrease in alternative prescriptions including anti-reflux and colic relief products, as well as lactose-free and partially hydrolyzed milks for underlying CMA. This study demonstrates both the need for health care provider education on gastrointestinal CMA as well as the usefulness of educational campaigns and national treatment guidelines.

Extensively hydrolyzed formulas are the first-line treatment for formula-fed infants with CMA. Older-generation extensively hydrolyzed formulas were typically free of lactose. In recent years, lactose has been added to extensively hydrolyzed formulas. Lactose in hydrolyzed formula has been shown to increase the absorption of calcium when compared to lactose-free formula.[44] Highly purified lactose is tolerated well by infants with CMA.[45,46] The addition of lactose slightly increases the sweetness of extensively hydrolyzed formula, which is thought to improve the overall palatability. This reduces the risk of taste aversion and formula refusal, particularly by older infants.[47] Lactose restriction is only warranted in infants with CMA if an enteropathy with secondary lactase deficiency is present. Lactose may cautiously be reintroduced after about 1 to 2 months, once symptoms have resolved and small intestinal lactase activity been restored.

CONCLUSIONS

Lactose intolerance is a non–immune-mediated AFR caused by absence of lactase, which causes the person to be unable to absorb the sugar present in cow's milk. CMA is an immune-mediated AFR, as it is the allergic reaction to a protein present in cow's milk. These conditions are similar in some points, such as in the symptoms, as both have gastrointestinal clinical presentation. Confusion between CMA and lactose intolerance may lead to a delayed diagnosis of CMA, as well as inappropriate dietary interventions with nutritional risks. As in all other fields of medicine, a good medical history and a physical examination are the first necessary component of a proper diagnostic process. The clinical history is, in most cases, pointing toward the possible offending food, but one must keep in mind that parent and patient reports of a food intolerance must be confirmed. Several diagnostic tests may be of help, and in the previous sections we indicated some for specific suspected conditions. The mainstay of treatment for AFRs is to remove the causative food from the diet. In the AFRs induced by CMA, even small protein doses can cause symptoms, so the management is based on the strict avoidance of the cow's milk-derived allergenic peptides from the diet. On the contrary, reduction of lactose intake, rather than full exclusion, is recommended in people with lactose intolerance. Evidence-based educational health campaigns are needed to avoid misunderstandings between lactose intolerance and CMA among patients and physicians.

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