

## Lactose malabsorption and intolerance: What should be the best clinical management?

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### Abstract

Lactose malabsorption (LM) is the incomplete hydrolysis of lactose due to lactase deficiency, which may occur as a primary disorder or secondary to other intestinal diseases. Primary adult-type hypolactasia is an autosomal recessive condition resulting from the physiological decline of lactase activity. Different methods have been used to diagnose LM. Lactose breath test represents the most reliable technique. A recent consensus conference has proposed the more physiological dosage of 25 g of lactose and a standardized procedure for breath testing. Recently a new genetic test, based on C/T13910 polymorphism, has been proposed for the diagnosis of adult-type hypolactasia, complementing the role of breath testing. LM represents a well-known cause of abdominal symptoms although only some lactose malabsorbers are also intolerants. Diagnosing lactose intolerance is not straightforward. Many non-malabsorber subjects diagnose themselves as being lactose intolerant. Blind lactose challenge studies should be recommended to obtain objective results. Besides several studies indicate that subjects with lactose intolerance can ingest up to 15 g of lactose with no or minor symptoms. Therefore a therapeutic strategy consists of a lactose restricted diet avoiding the nutritional disadvantages of reduced calcium and vitamin intake. Various pharmacological options are also available. Unfortunately there is insufficient evidence that these

therapies are effective. Further double-blind studies are needed to demonstrate treatment effectiveness in lactose intolerance.

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**Key words:** Lactose malabsorption; Lactose intolerance; Therapeutic options

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### INTRODUCTION

Lactose is the disaccharide found in milk and dairy products. Absorption of lactose requires lactase activity in the small intestinal brush border. Hypolactasia, or lactose malabsorption (LM), exists in three distinct forms: congenital, primary and secondary. Congenital lactase deficiency is associated with the least lactase activity. It is a lifelong disorder characterized by failure to thrive and infantile diarrhea from the first exposure to breast milk. Congenital hypolactasia, a single autosomal recessive disorder<sup>[1]</sup>, is extremely rare, with only around 40 cases having been reported.

Primary adult-type hypolactasia, an autosomal recessive condition resulting from the physiological decline of lactase enzyme activity in the intestinal cells, occurs in a large proportion of individuals. A single nucleotide polymorphism, C/T-13910, 14 kb upstream the lactase gene, has recently been correlated with lactase persistence/non persistence in several populations<sup>[2,3]</sup>. Secondary causes

of hypolactasia, such as celiac disease, gastroenteritis and Crohn's disease, may lead to transient lactase deficiency and appearance of abdominal symptoms similar to those of primary LM.

The onset of adult-type hypolactasia is correlated to age: lactase activity is highest at birth and declines after weaning<sup>[4,5]</sup>. The frequency of this condition varies according to ethnicity<sup>[6]</sup>, with reported lower prevalence in Northern Europe (< 5%), compared to Southern Europe (70%-80%) and Southeast Asia (almost 100%). LM represents a well-known cause of abdominal disorders, like diarrhoea, bloating, excessive flatus and abdominal pain. However, sugar malabsorption does not necessarily result in the development of intolerance symptoms; in fact, only about one-third to half of lactose maldigesters are also intolerants.

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## DIAGNOSIS OF LACTOSE MALABSORPTION

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Different methods have been used for the diagnosis of LM. Lactose activity assay by jejunal biopsy has been proposed as the "gold standard"<sup>[7,8]</sup>. However, it seems too invasive for the diagnosis of such a mild condition and its results may be influenced by the irregular dissemination of lactase activity throughout the small intestine mucosa. Lactose breath test (BT) represents an indirect test for LM, and it is commonly considered the most reliable, non-invasive and inexpensive technique<sup>[9]</sup>. However, it is possible to find false negative BTs, due to the inability of colonic flora to produce H<sub>2</sub> after ingestion of non-absorbable carbohydrates, or after a recent administration of antibiotics. False positive BTs are less frequent and are mainly produced because of small bowel bacterial overgrowth<sup>[4]</sup>. Reviewing methodological studies<sup>[3,7,8,10]</sup>, lactose BT shows good sensitivity (mean value of 77.5%) and excellent specificity (mean value of 97.6%).

A recent consensus conference on BTs<sup>[10]</sup>, has examined the methodological aspects of BTs, based on a systematic review of the literature. The following recommendations were suggested on how to perform lactose BT: test duration of 4 h (3 h for pediatric use), sample intervals of 30 min and a cut-off value of 20 ppm above the baseline. Finally a more physiological dosage of 25 g of lactose was recommended to be used for BT. In fact many studies of BT validation<sup>[7,8]</sup> have utilized the dosage of 50 g lactose (approximately corresponding to one liter of milk) which has been criticized because it represents an amount far higher than that usually ingested at any one time. Besides, patients with lactose intolerance (LI) may experience considerable discomfort with this dosage.

Recently, the C/T-13910 polymorphism roughly 14 Kb upstream of the lactase gene locus on chromosome 2q21, has been found to be completely associated with lactase activity<sup>[2]</sup> and proposed as a new diagnostic tool in adult-type hypolactasia<sup>[5,11]</sup>. Genomic DNA from patients may be obtained from peripheral blood samples, and DNA isolated using standard techniques<sup>[2,3,11]</sup>. Several

recent studies on adult subjects have demonstrated an excellent correlation between BT and the genetic test (GT) based on C/T-13910 polymorphism<sup>[3,11]</sup>. The absence of information on symptoms of intolerance represents the only diagnostic limit of GT.

A new LM diagnostic algorithm based on this information (Figure 1) has been proposed<sup>[11,12]</sup>: (1) The GT may complement in several aspects the BT, improving the diagnosis of adult-type hypolactasia. In all subjects with negative lactose BT, the GT provides an unambiguous result permitting the exclusion of false negative results (such as low hydrogen producers) and avoiding the need for further tests (lactulose or methane BTs); (2) Secondary causes of hypolactasia may be suspected in subjects with a positive BT and a C/T-13910 variant associated with lactase persistence; and (3) Finally, according to various studies<sup>[4,5]</sup>, the decline of lactase activity and the onset of adult-type hypolactasia should be evident from 8-12 years onwards. In younger subjects, the GT is not recommended, while the lactose BT remains of paramount utility in diagnosing secondary hypolactasia.

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## DEFINITION AND DIAGNOSIS OF LACTOSE INTOLERANCE

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It is important to distinguish between hypolactasia, a low level of lactase, and clinical LI. The likelihood that a lactose malabsorber will perceive symptoms after ingestion of lactose is a function of many variables, including the dosage of lactose, lactase activity of the mucosa, foods co-ingested with lactose, the lactose fermentation pathways of the colonic flora, and the visceral sensitivity of an individual's colon to LM. Many subjects diagnose themselves as being lactose intolerant. However, these self-identified lactose intolerant individuals may actually be lactase persistent. Some of those lactase persistent (and even lactase non-persistent) may mistakenly ascribe the symptoms of undiagnosed irritable bowel syndrome (IBS) or other intestinal disorders to LI<sup>[13-15]</sup>. Since the avoidance of milk and milk-containing products can result in a dietary calcium intake that is below recommended levels of 1 g per day for men and women and 1.3 g for adolescents, osteoporosis and associated fractures secondary to inadequate dietary calcium is the perceived major health risk associated with real or assumed LI<sup>[16,17]</sup>. Therefore we think that it is not sufficient to ask patients about the correlation between symptoms and lactose ingestion while an objective diagnostic test remains of paramount utility.

LI should be considered when ingestion of a single dose by a lactose malabsorber subject induces gastrointestinal symptoms not observed when the subject ingests an indistinguishable placebo. Although blind lactose challenge should be the recommended method, other methodological approaches have been considered to evaluate LI: non-blind lactose challenge and self-reported symptoms without lactose challenge<sup>[18]</sup>.

In fact, no studies of symptoms following blind lactose challenge are available, while only a few studies of

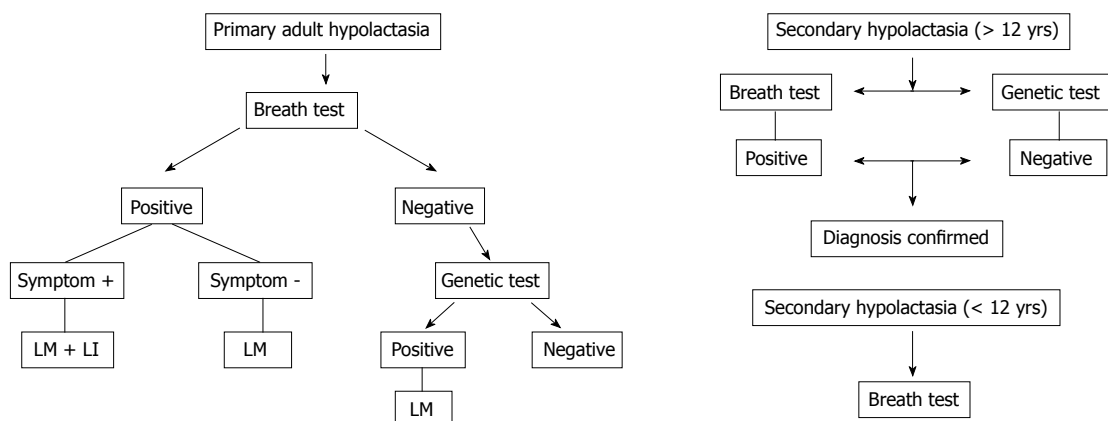


Figure 1 Diagnostic algorithm for suspected lactose malabsorption and intolerance. LM: lactose malabsorption; LI: Lactose intolerance.

Table 1 Treatment of lactose intolerance	
Non pharmacological options	
Milk with prehydrolyzed lactose	
Consumption of fermented and matured dairy products	
Ingestion of milk together with other foods	
Distribution in little meals of daily milk amount in snacks	
Colonic adaptation by increasing lactose load	
Pharmacological options	
Enzyme replacement with lactase supplements	
Probiotics	
Antibiotics	

Note: Calcium and vitamins support if daily intake is inadequate.

non-blind lactose challenge have been published with conflicting results. For African American, Hispanic, Asian, and American Indian populations LI rates may be 50%, higher in late childhood and adulthood<sup>[18,19]</sup>.

Seven studies of self-reported symptoms without lactose challenge can be identified<sup>[18,19]</sup>. US estimated prevalence of self-reported LI was 12%, with estimates of 8% in European Americans, 10% in Hispanic Americans, and 20% in African Americans. Overall, the prevalence of self-reported symptoms was typically lower than the prevalence of symptoms following a lactose challenge<sup>[18,19]</sup>. On the other hand the recording of symptoms, by hydrogen BT following lactose challenge, is commonly considered the most reliable diagnostic method in clinical practice<sup>[7-10]</sup>. Variability among scores of the severity and duration of symptoms can be found in the literature as well as a poor agreement on the quality and quantity of symptoms to be considered<sup>[3,10,15]</sup>. The recent Rome consensus conference proposed the recording and scoring of the following four symptoms during the test and 8 h after: abdominal pain, bloating, flatulence and diarrhea<sup>[10]</sup>. About 33%-97% of the patients, with a positive BT result, reported symptoms after lactose ingestion (lactose intolerants). On the other hand, 0-71% of the lactose absorbers also appeared to report symptoms<sup>[20]</sup>. Several studies indicated that subjects with LI can ingest up to 10-15 g of lactose (comparable to approximately one cup of milk), particularly if taken with food, with no or mi-

nor symptoms<sup>[18,19]</sup>. Thus, as recently suggested<sup>[21]</sup>, in the diagnosis of LI a 10-12 g lactose test should probably be substituted for the classic 25 g lactose BT. Moreover this dosage is more physiological and similar to that usually ingested at any one time.

## THERAPEUTIC MANAGEMENT

In patients with hypolactasia, treatment is considered exclusively in the presence of intolerance symptoms. The common therapeutic approach tends to exclude milk and milk products from the diet. However, this strategy may have serious nutritional disadvantages in reduced intake of substances such as calcium and vitamins. Therefore since there are no known adverse effects of LM other than gastrointestinal symptoms not all subjects with lactase deficit have to be treated, only symptomatic ones. Moreover it is necessary to distinguish between primary and secondary lactase deficiency. In the secondary form a temporary lactose-free diet is necessary only until a complete recovery of the causative pathological condition is obtained<sup>[22]</sup>. In primary hypolactasia, a temporary (2-4 wk) avoidance of milk and dairy products from the diet should be indicated to obtain symptom remission. Subsequently, a gradual re-introduction of low-lactose dairy products can be suggested, considering the individual threshold dose. In fact there may be sizable individual differences in the dose of lactose that can be tolerated by subjects with LI. In order to raise the threshold dose, both non-pharmacological and pharmacological strategies may be considered (Table 1).

### Non-pharmacological approach

Treatment to reduce lactose exposure, while maintaining calcium intake from dairy products, consists of a lactose restricted diet or the use of milk in which the lactose has been pre-hydrolyzed via treatment with lactase supplements<sup>[18,22,23]</sup>. Ingestion of milk together with other foods, consumption of fermented and matured dairy products, distribution in milky snacks, are other known methods. Another attractive approach in the management of LI is to increase the lactose load giving the colon time to

adapt<sup>[18,22,24,25]</sup>. This is supported by the observation that introduction of lactose to the diet causes temporary and transient symptoms in individuals. Since lactase from intestinal brush border is not an inducible enzyme, the reduction in symptoms may be explained by colonic adaptation.

### Pharmacological approach

Enzyme replacement therapy with lactase from nonhuman sources to hydrolyze lactose is another important approach to preventing LI. There are multiple commercially available lactase supplements containing variable amounts of beta-galactosidase from a variety of sources<sup>[18,22,26]</sup>.

Probiotics are live microorganisms that are nonpathogenic and have beta-galactosidase or lactase intracellularly and may aid in the digestion of lactose ingested by the host. These microorganisms can be added to food products, such as milk and yogurt, or used as supplements. Examples of commonly used probiotics include lactobacillus, bifidobacterium, and saccharomyces<sup>[18,22,27]</sup>.

Other strategies for management of LI include gut decontaminating agents and anti-microbials, such as rifaximin<sup>[18,28]</sup>.

However, a recent systematic review<sup>[19]</sup> has examined the management strategies for LI. There was not sufficient evidence that lactose-reduced solution or milk with a lactose content of 0 to 2 g, compared with greater than 12 g, is effective in reducing symptoms of LI. Evidence for lactase supplements, probiotics, colonic adaptation, and other agents was also insufficient.

### CONCLUSION

LM is the most common type of carbohydrate malabsorption and is caused by low lactase levels. Several diagnostic methods are available for the diagnosis of LM. Recently, the Rome Consensus Conference confirmed the diagnostic validity of lactose BT and proposed a more physiological lactose dose in standardized conditions. Besides the recent introduction of a new GT, correlated with lactase persistence /non-persistence and based on C/T13910 polymorphism, may improve the diagnosis of adult-type hypolactasia, complementing the role of BT. When lactose malabsorption gives rise to symptoms, this is called LI. Diagnosing LI is not straightforward. Many subjects diagnose themselves as being lactose intolerant. However, these individuals may actually be lactase persisters and mistakenly ascribe the symptoms of IBS to LI. Blind lactose challenge should be the recommended method to evaluate LI, but there is no data available either in the literature or in clinical practice regarding its adoption.

Most individuals with presumed LI can tolerate up to 15 g of lactose. As the dose is increased above 15 g, several therapeutic options may be proposed.

Treatment to reduce lactose exposure consists of a lactose restricted diet or the use of lactase supplements. Other strategies include probiotics, colonic adaptation

and antibiotics. Unfortunately there is insufficient evidence that these therapies are effective for LI. A major number of double-blind, placebo-controlled studies should be conducted to evaluate treatment effectiveness in individuals with well-documented LI.

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