

# What do we know about lactose?



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There is much confusion between the diagnostic terms 'lactose intolerance' and 'cows' milk allergy', which are often used interchangeably,<sup>1</sup> resulting in the potentially incorrect clinical management of these two distinct conditions.<sup>2</sup>

Parents and health professionals alike frequently exclude lactose from an infant's diet in an attempt to treat symptoms involving loose stools and colic, whether this is thought to be due to cows' milk allergy, lactose intolerance or both. This practice may be short-sighted as the inclusion of lactose in the diet is suggested to offer a number of advantages, including better palatability of infant formula, better absorption of certain micronutrients, and potential contribution to the development and maintenance of a healthy gut mucosa, microbiome and immune system.

This article aims to provide an overview of what we know about lactose, its potential benefits in the diets of infants and young children and the diagnosis and management of varying conditions associated with lactose intolerance.

## What is lactose?

Lactose is a disaccharide and the predominant sugar found exclusively in the whey of mammalian milks and milk products.<sup>3,4</sup> Breast milk and, consequently, infant formula – the composition of which is based on breast milk – are extremely rich sources of lactose and contain over 50% more lactose than that found in cows' milk.<sup>5</sup> It is digested by the enzyme lactase (a  $\beta$ -D-galactosidase with the full name 'lactase-phlorizin hydrolase') into the simple sugars glucose and galactose, which are rapidly absorbed for effective energy utilisation.<sup>3,4</sup> Lactase is found in the tips of the intestinal villi of the small intestinal brush border and is particularly vulnerable to immune-related intestinal mucosal injury.<sup>3,4</sup> If lactase activity is low or absent, undigested lactose passes through the small intestine into the colon, where it may induce symptoms typically associated with lactose intolerance.

## Benefits of lactose in infants and young children

### Palatability

Lactose is only half as sweet as glucose and around a sixth of the sweetness of sucrose, making it very palatable.<sup>5</sup> The presence of lactose in whey-based extensively hydrolysed infant formula, used for the management of infants with cows' milk allergy, has been shown to make these naturally strong, bitter tasting formula (due to the presence of short chain peptides) more palatable.<sup>6,7</sup>

### Increased mineral absorption

Lactose containing infant formula have been shown to significantly improve the absorption of calcium<sup>8,9</sup> and other micronutrients, including magnesium and manganese.<sup>9</sup>

“Lactose is a disaccharide and the predominant sugar found exclusively in the whey of mammalian milks and milk products.<sup>3, 4</sup>”

### Effects on the gut microbiome and immune system

Unhydrolysed lactose is considered to be a prebiotic in young infants;<sup>10</sup> defined as a non-digestible food ingredient that beneficially affects host health by selectively stimulating the growth and/or activity of one or more of a limited number of bacteria in the colon.<sup>11</sup> A study by Francavilla and colleagues demonstrated that the presence of lactose in infant formula resulted in an increase in the commensal bacteria *Bifidobacteria* and *Lactobacilli*, supporting this theory that lactose is a prebiotic.<sup>12</sup> Commensal bacteria are considered to be probiotics in accordance with the joint World Health Organization (WHO)/Food and Agricultural Organization (FAO) of the United Nations, if when administered live as part of a food they confer a beneficial health effect via modification of the host's intestinal microbiome.<sup>13</sup> In this study, the increase in probiotic bacteria was accompanied by a reduction in the potential pathogenic bacteria - *Bacteroides* and *Clostridia* - and an increase in the concentration of short chain fatty acids (SCFA).<sup>12</sup>

Lactic acid bacteria are Gram-positive and include the genus *Lactobacillus*, *Bifidobacterium*, *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Leuconostoc* and *Pediococcus*. They all ferment lactose to produce lactate, hydrogen, methane, carbon dioxide and SCFA.<sup>14</sup> Lactic acid bacteria in the colon contain microbial lactase which is capable of hydrolysing some of the malabsorbed lactose into its component monosaccharides, which are then absorbed or fermented.<sup>5</sup> This is less likely to occur as the pH falls, but a lower pH favours lactic acid bacteria over potential pathogens.<sup>3</sup>

Short chain fatty acids produced from lactic acid bacterial fermentation include acetate, a substrate for colonic epithelial cells, enabling the salvage of energy which can be around 5-15% of the total energy requirements of an adult.<sup>15</sup> It is believed that butyrate, another SCFA, stimulates the growth of enterocytes and plays a role in prevention of colonic inflammation and oxidative stress.<sup>16</sup> SCFA have also been shown to improve the colonic defence barrier, leading to enhanced protection against luminal antigens.<sup>16</sup> They are involved in the strengthening of the mucous layer of the epithelial lining via effects on mucin glycoproteins impeding microbiota from penetrating the inner epithelium, and promote production of antimicrobial proteins, which are part of the defensin

protein family, which have the capacity to kill bacteria by compromising bacterial cell wall integrity.<sup>17</sup>

*Bifidobacteria* and *Lactobacilli* may protect against the development of atopy and allergy via their effects on the immune system. Commensal bacteria in the gut are genetically programmed not to express factors that enable cell invasion, whereas pathogenic bacteria are able to invade cells and combat antimicrobial defences of the host.<sup>17</sup> *Bifidobacteria* have been shown to induce secretory IgA, which is produced by B cells in the gut associated lymphoid tissue (GALT) and secreted across the epithelial wall.<sup>18</sup> Gut secretory IgA is thought to be involved in trapping bacteria in the mucus layer preventing pathological invasion, thereby maintaining the normal host-microbiota balance. It may also play a role in oral tolerance through binding of antigens in the gut and preventing systemic uptake of the antigen. Food allergy rates have been shown to be higher in children with IgA deficiency.<sup>17</sup>

Gut microbiota is one of the environmental signals that promote T-cell maturation, via induction of T regulatory (Treg) cells in GALT.<sup>19</sup> During pregnancy, the Th1 immune response of the foetus is suppressed to prevent excessive response to maternal antigens, resulting in a skew towards Th2. Enhanced responses from Th2 cells are associated with production of interleukin (IL)-4, IL-5, IL-9 and IL-13, which contribute to allergic inflammation and disease. Exposure to commensal gut microbiota during the early postnatal period however, shifts this response to development of Th1 cells and expression of the anti-inflammatory cytokine IL-10, which promotes immune tolerance and maintains a Th1/ Th2 balance.<sup>17</sup> Immune tolerance is the ability of the immune system to recognise a harmless antigen and actively suppress an inflammatory response.<sup>17</sup> Commensal bacteria balance the generation of pro- and anti-inflammatory cytokines in the gut, and probiotics have been shown to downregulate inflammatory mediators, such as tumour necrosis factor (TNF- $\alpha$ ) and faecal  $\alpha$ -1 anti-trypsin, and stimulate anti-inflammatory effects of toll-like receptors (TLR).<sup>19</sup>

Lactose therefore has the potential to indirectly enhance the immune system via positively influencing the composition of the gut microbiota and increasing production of SCFA. It does raise the question as to whether incomplete digestion of lactose in the early post-natal period is part of a natural physiological

phenomenon. Francavilla and colleagues have expressed interest in determining whether lactose may play a role in the acquisition of immune tolerance.<sup>12</sup>

### What is lactose intolerance?

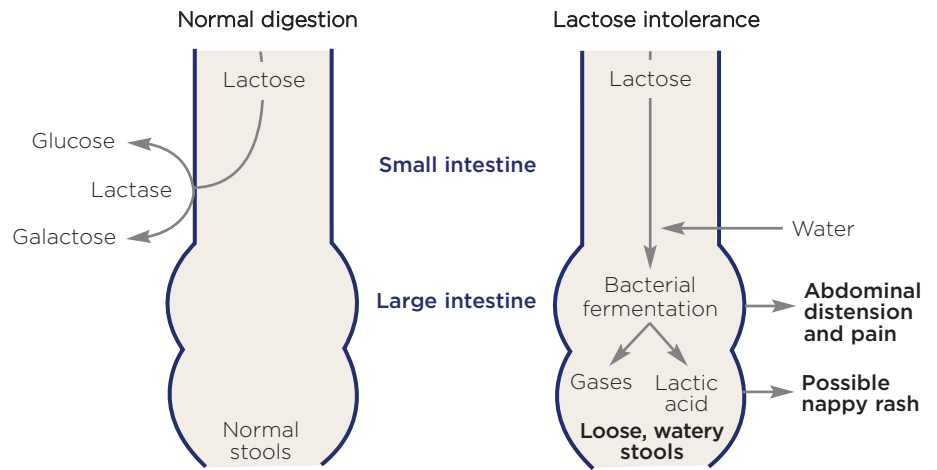
Lactose intolerance is a physiological response to undigested lactose in the colon, resulting from lactase inactivity or deficiency.<sup>3-5</sup> As illustrated in **Figure 1**, abdominal pain and bloating occur as a result of colonic fermentation of unabsorbed lactose by lactic acid bacteria, associated with production of SCFA, lactic acid, hydrogen, carbon dioxide and methane gases.<sup>5</sup> Occasionally, gastrointestinal motility is reduced as a result of methane production and subsequently a few cases may suffer from constipation.<sup>21</sup> More typically, however, unfermented lactose and lactic acid increase the osmotic load, resulting in greater secretion of electrolytes and fluid into the colon and exacerbation of abdominal distension.<sup>5</sup> Due to the nature of these products and their effect on speeding up gut transit, the well-recognised symptoms of acidic, loose, watery stools ensue, often accompanied by nappy rash in infants. These symptoms can be acute and severe and can cause significant dehydration.

It is helpful to consider lactose intolerance as a spectrum involving a variety of underlying causes for the condition. **Table One** identifies five distinct conditions associated with lactose intolerance.

### Developmental lactase deficiency

By week eight of gestation, lactase activity can be detected at the mucosal surface in the human intestine. The greatest increase in lactase occurs during the third trimester when activity increases 3 to 4-fold, and it has been demonstrated that the digestion of lactose is not complete in the preterm infant.<sup>22</sup> Whilst studies in adults have shown that lactase activity cannot be induced by feeding lactose,<sup>23</sup> it has been shown that early feeding with lactose-containing formula from day four of life in preterm infants resulted in an earlier increase in lactase activity compared with those who started enteral feeds later.<sup>24</sup> The same authors have since demonstrated that maturational changes in lactose digestion and absorption appear more related to an increase in lactase specific activity than to a general increase in small-intestinal mucosal growth.<sup>22</sup>

Figure 1: Symptoms of Lactose Intolerance



Reproduced from reference 20.

Table One: Spectrum of Conditions Associated with Lactose Intolerance (LI)

Lactose intolerant condition	Key points and treatment
<b>Congenital lactase deficiency</b>	<ul style="list-style-type: none"> <li>Extremely rare</li> <li>Characterised by faltering growth and intractable diarrhoea as soon as milk is introduced</li> <li>Life threatening due to dehydration &amp; electrolyte losses</li> <li>Strict lifelong lactose free diet</li> </ul>
<b>Developmental lactase deficiency</b>	<ul style="list-style-type: none"> <li>Lactase is deficient until at least 34 weeks gestation</li> <li>Up to 20% of dietary lactose may reach colon in young infants and favour growth of probiotic bacteria</li> <li>May have a role in infantile colic – undertake a 1 week empirical trial using lactase drops. Continue until 4 months of age, then wean off</li> </ul>
<b>Secondary LI post gastroenteritis (acute acquired lactase deficiency)</b>	<ul style="list-style-type: none"> <li>Acute gastro-intestinal (GI) infection can cause small intestinal injury with loss of lactase</li> <li>At risk infants are those under 3 months of age or malnourished</li> <li>6-8 week exclusion of lactose, using a low lactose infant formula then regrade onto normal infant formula</li> </ul>
<b>Secondary LI due to CMA &amp; other enteropathies (chronic acquired lactase deficiency)</b>	<ul style="list-style-type: none"> <li>If no recent episode of gastroenteritis, or unable to regrade onto normal infant formula post GI illness, immune-related enteropathy most likely cause, e.g. cows' milk allergy (CMA), coeliac disease</li> <li>Take an allergy focused clinical history</li> <li>If CMA is likely, undertake a 4 week exclusion trial of cows' milk using a hypoallergenic formula, then re-challenge to confirm diagnosis</li> </ul>
<b>Primary lactose intolerance (lactase non-persistence)</b>	<ul style="list-style-type: none"> <li>Rare in children under 2-3 years of age</li> <li>Common worldwide but significant differences linked to ethnic origin</li> <li>Gradual loss lactase with age</li> <li>Reduced lactose containing diets necessary, based on individual levels of tolerance</li> </ul>

“Lactose intolerance is a physiological response to undigested lactose in the colon, resulting from lactase inactivity or deficiency.<sup>3-5”</sup>

Whilst the presence of lactose in the colon seems to be of benefit to infants due to its effects on the gut microbiome, there may be a group of infants who are unable to tolerate the high lactose load and who, consequently, present with infantile colic. Colic can be used as an acronym to represent the core symptom of excessive crying ‘Cause Obscure Lengthy Infant Crying’.<sup>25</sup> There are many potential underlying causes of colic, including cows’ milk allergy, transient lactose intolerance, hyperalgesic colonic hyperperistalsis, imbalance in gut microbiota, disrupted parent-infant interactions, gastro-oesophageal reflux disease, constipation<sup>26</sup> and infant migraine,<sup>27</sup> making it very difficult to produce well-powered randomised controlled intervention trials. As a result, all organic causes should be ruled out via a detailed clinical, feeding and behavioural history before embarking on empirical trials of various remedies/treatment options.<sup>26</sup>

Infante and colleagues explored the effects of a reduced lactose formula on excessive gas production in a group of infants with symptoms of excessive flatus, watery/frothy stools, audible bowel sounds (borborygmi) and distress during feeding and excluded those with symptoms suggestive of cows’ milk allergy, gastro-oesophageal reflux or those with constipation.<sup>25</sup> They demonstrated that when using a reduced lactose formula (3% lactose compared with 7% in normal infant formula), levels of expired hydrogen and degree of flatulence decreased, accompanied by a reduction in infant crying.<sup>25</sup> This supports the earlier findings of Kanabar and colleagues who used lactase enzyme, which reduces lactose content by about two thirds.<sup>28</sup> It has previously been shown that the typical time for onset and resolution of symptoms of colic in infants are mirrored by the onset, peak and resolution of abnormal hydrogen breath tests.<sup>29</sup>

It is important to note that these intervention studies used formulas with a reduced lactose load as opposed to low lactose formula, due to awareness of the benefits of lactose on calcium absorption and the absorption capacity in young infants of 4.5 g/kg/d.<sup>25</sup> The revised NICE Clinical Knowledge Summaries (CKS) on infantile colic recommend a one week trial using lactase enzyme, but not a low lactose infant formula.<sup>30</sup> If it works, they recommend weaning off around three to four months and no later than six months.

## Secondary lactose intolerance post gastroenteritis (acute)

Acute infection (e.g. rotavirus) can cause small intestinal injury accompanied by loss of lactase-containing epithelial cells from the tips of the villi.<sup>3</sup> The immature epithelial cells that replace them are often lactase deficient, resulting in lactose malabsorption and subsequent symptoms (**Figure 1**). Only 50% of lactase activity however, is required for adequate lactose digestion<sup>31</sup> and hence the typical practice of using a low lactose formula for 6-8 weeks in accordance with the World Health Organisation<sup>32</sup> for persistent post-infectious diarrhoea (diarrhoea lasting more than 14 days) is not thought to offer any clinical advantage in well-nourished infants who have mild or little sign of dehydration. Those at greatest risk are infants younger than three months and those who are severely malnourished who develop small intestinal atrophy.<sup>3</sup>

Whilst it is recommended that lactose intolerance is formally diagnosed by using either a hydrogen breath test, lactose tolerance test or stool testing for reducing substances and pH,<sup>4</sup> they can be difficult to do in young children, especially in the community.<sup>2</sup> As a lactose exclusion trial is required to confirm the diagnosis, the preferred option is to empirically undertake the exclusion trial followed by reintroduction, which also helps to determine how much lactose can be tolerated by the individual.<sup>2</sup>

The important point to remember is that if symptoms do improve on a reduced/low lactose formula and diet, it is only an acute episode and that once the new epithelial cells on the villi recover, lactose intolerance should resolve. It is, therefore, imperative given the potential benefits of lactose to ensure that infants do not remain on a lactose restricted diet for longer than a 6-8 week period, and that they are graded back onto a normal diet over 1-2 weeks.

## Secondary lactose intolerance due to enteropathy (chronic)

If the infant has failed to regrade back onto normal infant formula after a 6-8 week period of lactose exclusion, there is likely to be an underlying enteropathy, the most common in infancy being cows’ milk allergy.<sup>2,3</sup> Other conditions where this can occur are in children with coeliac disease, inflammatory bowel disease and following treatment with chemotherapy.

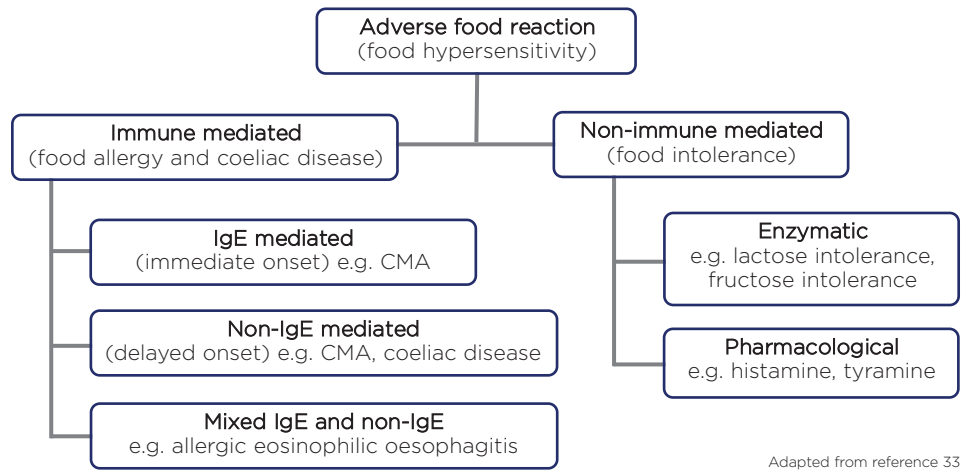


In these cases, lactose elimination should not be necessary once the underlying condition has been treated.<sup>2,3</sup>

Lactose intolerance is distinctly different from cows' milk allergy, which involves the immune system and can cause immediate reactions such as urticaria and anaphylaxis or more delayed reactions which often involve intestinal mucosal injury (Figure 2). It is this latter group of non-IgE mediated allergic reactions to cows' milk that is frequently confused with lactose intolerance.

Diagnosis of food allergy relies heavily on a thorough allergy focused clinical history, which concentrates on the three key organ systems; gut, skin and respiratory alongside family and personal history of atopy and allergy.<sup>34, 35</sup> As Figure 2 depicts, non-IgE mediated cows' milk allergy is an immune-related disorder involving type IV cell mediated mechanisms, whereas lactose intolerance does not involve the immune system. As a result, the total range of symptoms exhibited is much broader in infants with cows' milk allergy compared with lactose intolerance (Table Two). Whilst there is a common core of gut-related symptoms, some of which may actually be due to secondary lactose intolerance in infants with cows' milk allergy, there are usually additional red flag symptoms present indicative of immune system involvement, such as mucous in the stools, eczema, rhinitis and/or family history of food allergy and atopy.<sup>34</sup> The following case study illustrates these points.

Figure 2: Classification of Food Hypersensitivity



Adapted from reference 33

Table Two: Symptomatology of Lactose Intolerance and Cows' Milk Allergy

Symptoms of lactose intolerance	Symptoms of cows' milk allergy (CMA)
<ul style="list-style-type: none"> <li>Loose, watery, frequent stools</li> <li>Abdominal pain and distension</li> <li>Excessive flatulence</li> <li>Audible bowel sounds (borborygmi)</li> <li>Infantile colic</li> <li>Nappy rash</li> </ul>	<ul style="list-style-type: none"> <li>Loose, watery, frequent stools</li> <li>Abdominal pain and distension</li> <li>Excessive flatulence</li> <li>Audible bowel sounds (borborygmi)</li> <li>Infantile colic</li> <li>Nappy rash</li> </ul>
<p><b>Less common:</b></p> <ul style="list-style-type: none"> <li>Constipation</li> <li>Nausea and vomiting</li> </ul>	<ul style="list-style-type: none"> <li>Mucousy, bloody or offensive stools</li> <li>Constipation</li> <li>Vomiting or gastro-oesophageal reflux</li> <li>Poor weight gain</li> <li>Food refusal</li> <li>Eczema</li> <li>Other atopic conditions such as hay fever, runny or congested nose, wheeze or cough, hives (urticaria) or swelling (angioedema), anaphylaxis</li> <li>Family history of cows' milk allergy</li> </ul>

### Case study

A three-month-old Asian girl had a history of loose, watery, offensive, mucousy stools, excessive flatulence, distress, vomiting, poor sleeping and feeding, mild eczema and nasal congestion. There is a family history of lactose intolerance in mum as a baby and she outgrew it around two years of age. Mum introduced her to a range of different formulas, including a partially hydrolysed, lactose reduced comfort milk which helped somewhat, but her gut symptoms only really improved once she started a low lactose formula. However, following an allergy focused clinical history it was noted that she was still suffering from some dry skin, congestion, had some intermittent mucous in her stools and remained a poor feeder. She was referred to the dietitian due to her poor feeding.

She was advised to regrade onto normal formula, as lactose intolerance should only be a transient condition in infants and children under 2-3 years of age, whatever their ethnicity.<sup>2,3</sup> Her symptoms returned and so she was informed that this was likely to be lactose intolerance secondary to cows' milk allergy and that

mum was also likely to have had cows' milk allergy as a child. She was therefore advised to change the formula to an extensively hydrolysed formula, with preference for one containing some lactose if tolerated due to its potential benefits and the fact it is not thought to pose a problem for the majority of infants with cows' milk allergy.<sup>36</sup> Due to her increasing age and potential palatability issues, she was advised to grade onto this over a week with her current formula, and cows' milk free weaning advice was provided for the future.

She tolerated the formula despite it containing some lactose and took to solids well. Her dry skin and congestion resolved, there were no more signs of mucous and generally she was more settled. A re-challenge with cows' milk in the form of a Lactofree™ yogurt (contains cows' milk protein but is lactose free) was undertaken around eight months of age, to which she did react, confirming for the family and GP the diagnosis of non-IgE mediated cows' milk allergy as opposed to lactose intolerance. A cows' milk challenge starting with baked foods containing cows' milk was recommended at one year of age, to determine whether she had developed a degree of tolerance to cows' milk.

\* In children with a history of more severe diarrhoea and nappy rash, a lactose free extensively hydrolysed formula may be advisable until resolution of symptoms occurs, followed by conversion to one containing some lactose.<sup>2,35</sup>

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## Primary lactose intolerance

Lactase non-persistence is rarely seen in children under 2-3 years of age, but it is common however, with approximately 70% of the world's population suffering from the condition.<sup>2,3</sup> The prevalence of the condition is genetically determined and associated with large ethnic differences relating to the use of dairy products in the diet.<sup>3, 31</sup> As a result, primary LI is only seen in 2% of northern Europeans but almost 100% of Asian and American Indian people.<sup>3, 31</sup> The age of onset also varies, with 80-90% of Chinese and Japanese children losing lactase activity by 3-4 years of age. Onset of primary LI has been seen in Thai children as early as 1-2 years of age, whereas it tends to develop in adolescence in white populations, associated with a gradual loss of ability to produce lactase over time.<sup>2,3</sup>

Primary LI involves lifelong avoidance of foods containing high levels of lactose, although most can tolerate small amounts of lactose in foods and medications. **Table Three** highlights lower lactose alternatives to lactose rich containing foods. Given the potential benefits of lactose however, individuals should be encouraged to include products containing lactose as far as they can tolerate.<sup>3,5</sup> Re-introduction of lactose has been shown to help decrease symptoms of lactose intolerance, which may be linked to the prebiotic effects of lactose.<sup>37</sup>

Whilst up to 240 ml cows' milk (12 g lactose) is often well tolerated if spread throughout the day,<sup>5</sup> Lactofree™ products help to ensure that individuals continue to receive an intake of all the nutrients that they would obtain on a normal cows'

milk containing diet whilst avoiding lactose, so there should be no nutritional concerns in those who consume these as part of their daily diet. Plant-based milks however are naturally lower in a number of nutrients compared with cows' milk; in particular energy, protein, vitamin A, riboflavin, iodine and calcium, although a number of the milks are fortified with calcium, and alternative sources of these nutrients should be sought.

## Conclusion

There is common confusion between the terms lactose intolerance and cows' milk allergy. As primary lactose intolerance in children under three years of age is rare, lactose intolerance is more likely to be secondary to mucosal injury, resulting from either a gastrointestinal illness or an enteropathy such as non-IgE mediated cows' milk allergy or coeliac disease. An allergy focused clinical history is essential to help determine whether food allergy is likely.

Lactose enhances calcium absorption and improves the palatability of infant formula. Lactose may support growth of commensal bacteria which in turn may influence gut integrity, inflammation and allergic disease. Given these potential benefits, it is recommended to consider including lactose in the diet of those needing to restrict cows' milk, to a level tolerated by the individual. In those with cows' milk allergy and diarrhoea, if a low lactose extensively hydrolysed formula is considered necessary at the outset, it would be advisable to review the suitability of progressing onto an extensively hydrolysed formula containing lactose once symptoms have resolved.

**Table Three: Sources of Lactose and Lower Lactose Alternatives**

Rich sources of lactose <sup>5</sup>	Lower lactose alternatives
Breast milk	Colief™ added to breast milk or infant formula, low lactose infant formulas, 'comfort' infant formula milks
Cow and goat milk-based infant formula	Lactofree™ milk, plant-based milks
Cow, goat and other mammalian milks	Butter, Lactofree™ cream, plant-based creams
Yogurt/fromage frais	Lactofree™ yogurt, plant-based yogurts
Cheese – especially soft and processed	Hard, mature cheese, e.g. cheddar, parmesan, Lactofree™ cheese, plant-based (vegan) cheese
Milk-based puddings, e.g. custard, ice cream	Plant-based milk puddings, i.e. those made with plant-based or Lactofree™ milk