Redefining lactose as a conditional prebiotic

Andrew Szilagyi MD FRCP

Lactose malabsorption and intolerance was initially described in the 1960s. Symptoms of gas, cramps, bloating and diarrhea resembled those sustained in irritable bowel syndrome (IBS), and for the first time a possible biochemical explanation for this elusive condition became available (1). The notion that lactose intolerance is responsible for IBS has captured the public imagination and spawned the introduction of lactose-free products and digestive enzymes. The extent and significance of the public interest of this association is attested to by the listing of over 72,000 internet sites on lactose intolerance. However, the prevailing view was perhaps based on insufficiency of evidence of therapeutic probiotic benefit with gastroenteritis (especially rotavirus) (7,8) recurrence of antibiotic-associated diarrhea (9), pouchitis (10,11) and emerging studies with inflammatory bowel diseases (IBD) (12,13).

In parallel with the understanding of bacterial and host communications, the medical use of probiotics has emerged as a plausible therapeutic option (6). There is reasonably good evidence of therapeutic probiotic benefit with gastroenteritis (especially rotavirus) (7,8) recurrence of antibiotic-associated diarrhea (9), pouchitis (10,11) and emerging studies with inflammatory bowel diseases (IBD) (12,13).

Another area of advance has been made in the field of prebiotics, which is defined by Gibson and Roberfroid (14) as "a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improves host health." Table 1 lists the characteristics of prebiotics as defined by these authors. Table 2 lists a number of prebiotics, most of which are manufactured or derived from foods. It should be noted that at least three (transgalacto-oligosaccharides, fucogalactooligosaccharides and lactulose) are derived from lactose. Among these sugars, perhaps lactulose (galactose fructose) resembles lactose the closest (15-17). Lactulose is probably the first manufactured prebiotic. Originally, it was used for constipation and the treatment of hepatic encephalopathy (17). Subsequently, other benefits were ascribed to lactulose (18). Lactulose was slowly recognized as a prebiotic because many of its effects are associated...
with altered metabolism by resident flora and with expansion of selective, putatively beneficial, bacteria of *Bifidobacteria* species (17,18).

In this article I will argue that the original lactose in lactase insufficient subjects exerts prebiotic effects. This is a composite hypothesis based on the observation and thinking of a number of different groups (18,24). The objective is to fit lactose point by point into Gibson and Roberfroid’s (14) definition of a prebiotic.

**CHARACTERISTICS OF PREBIOTICS**

**Nonhydrolysis and nonabsorption in the upper gastrointestinal tract**

While all animals and humans are born with the ability to digest lactose, intestinal lactase levels decrease after weaning in all except approximately 25% to 30% of humans. This human dichotomy is achieved through genetic control, mostly at the transcription and some at the translational level (25). Lactase persistence (LP) is dominant while lactase nonpersistence (LNP) is autosomally inherited. Most genetically ordained LNP subjects lose approximately 90% of intestinal lactase in early to midchildhood (depending on ethnicity) (18,26). While in animals lactase may be induced by continued consumption of lactose, in humans this phenomenon has not been observed (27). As a result, 70% to 75% of the population is left with a permanent loss of lactase; because of this genetic dichotomy, it is likely that lactose consumption has a clear relationship with LNP status. In general, LNP subjects consume less lactose. Proof of nonhydrolysis in LNP subjects can be measured with a variety of tests and also may result in uncomfortable symptoms (18). However, it has been clearly shown that they can tolerate 250 mL to 500 mL of milk (approximately 25 g lactose) without any difficulty (28,29). More likely, altered consumption of lactose is affected by cultural practices. The inability to digest lactose in the face of continued consumption sets up conditions for possible prebiotic effects which could therefore be considered conditional. Whether massive doses of lactose in LP subjects could potentially exert a spillover effect similar to resistant starch has not been formally studied.

**Selectivity of flora, growth and metabolic activation**

The industrial aim of designing prebiotics is to selectively feed putative beneficial bacteria in the lower intestine. The current gold standard beneficial of targeting are species of *Bifidobacteria*. However, many other bacteria may exert beneficial effects and in fact controlled trials with probiotics for gastrointestinal diseases show proof of efficacy for *Lactobacillus GG* (rotavirus gastroenteritis (8) and relapse of antibiotic-associated diarrhea) (9), *Escherichia coli* strain Nissle (a nonpathogenic *Escherichia coli*) in ulcerative colitis (30) and a mixture of *Lactobacillus*, *Bifidobacteria* and one strain of *Streptococcus salivarius* subspecies thermophilus (VSL3, VSL Pharmaceuticals Inc, USA) in pouchitis (10,11) and IBD (13).

There are few studies which examine fecal bacterial effects of chronic lactose consumption in LNP subjects. However, there are laboratory and clinical studies which circumstantially suggest that desired targeted bacteria, *Bifidobacteria* and *Lactobacillus* are indeed stimulated to grow and are metabolically activated.

There are numerous lactose fermenting species of bacteria in the lower intestine. However, Hill (20) hypothesized that lactic acid bacteria are selectively stimulated by chronic lactose feeding. Indeed, a study by Ito and Kimura (22) showed that despite the ability to ferment lactose, *Bacteroides* and *Clostridia perfringens* (log10) colony counts decreased in the stool of LNP volunteers who were given 15 g/day of lactose. Colony counts of *Lactobacillus* significantly increased along with counts of *Staphylococcus*, *Candida* and *Enterococci*. There was also a nonsignificant increase in *Bifidobacteria* counts. However, because total bacteria also decreased, there was a significant proportional increase in *Bifidobacteria* ratios (22).

As stated, lactulose is quite similar to lactose, and interestingly a bacterial profile in response to chronic 3 g/day lactulose feeding also led to decreased *Bacteroides* and *C. perfringens* populations (31). *Bifidobacteria* significantly increased (31,32) while *Lactobacillus* significantly decreased (31). However an earlier study in cirrhosis did show increased fecal *Lactobacilli* counts (33). While these results are not identical, they show that adaptation occurs to either lactose or lactulose resulting in elevation of desired target bacteria (note that lactulose is an accepted prebiotic).

The clinical features of colonic bacterial adaptation after prolonged sugar consumption is distinguished by diminished measured breath hydrogen and, likely, improved symptoms on rechallenge with standard doses of the sugar in question (23,34). This reduction was initially reported by Pernan et al (35) to be due to fecal acidification induced by metabolism of the test sugar (lactulose) to short chain fatty acids (mainly acetate). Fecal pH decreased to below pH 6 in volunteers and in vitro infusion studies on feces showed that fermentation was inhibited at this low pH. Pernan et al did not measure fecal bacteria or fecal β-galactosidase. Hertzler and Savaiano (23) were able to demonstrate improved lactose intolerance in LNP volunteers using increased lactose doses up to 1 g/day over 16 days. The adaptation was accompanied by the expected reduced breath hydrogen and as well a threefold increase in fecal β-galactosidase. In fecal infusion studies (while maintaining a near neutral pH), they were able to show that hydrogen production decreased while infused lactose consumption was completed (36). In another in vitro study, Jiang and Savaiano (37) showed that when pH was held constant there was complete consumption of infused lactose up to 25 g. However, infusion of 30 g overwhelmed and diminished the quantity of lactose consumption. This in vitro system was facilitated by the addition of Lactobacilli but only for the first of seven days. In vitro β-galactosidase increased 20-fold. Another study confirmed, just as Pernan et al (35) had shown, that in vitro lactose consumption was pH dependent. At near neutral pH, but not low pH, the addition of *Bifidobacteria* in vitro facilitated lactose consumption throughout a period of 72 h. Nevertheless, the authors postulated that the healthy colon absorption of short chain fatty acids and the secretion of bicarbonate likely compensated somewhat for the disaccharide-induced decrease in pH (38).

The demonstration that chronic lactulose feeding in subjects improves parameters of lactose intolerance suggests again that similar mechanisms exist between the probable prebiotic (lactulose) and the contender, lactose (39). Interestingly I also found a threefold increase in fecal β-galactosidase at a dose of 10 g twice daily of lactulose. The maximum single dose of lactose digested by remaining intestinal lactase in most LNP subjects is still unclear. However, in Japanese subjects this value may be 10 g (Dr T Oku, Siebold University, Nagasaki, Japan,
production with enhanced nitrogen consumption by specific bacteria (24, 45, 46). Moreover, the PSE therapeutic effect is also reproduced by feeding Enterococci faecium (47) and possibly by other Gram-positive anaerobes since these also produce less ammonia (31, 32, 46). As stated above, both Bifidobacteria and Lactobacillus seem to be quantitatively expanded by lactulose.

More than 23 years ago Uribe et al (48) showed that in LNP Mexican subjects lactose was more efficient in improving PSE than neomycin. They subsequently showed microbial alteration in fecal flora similar to lactulose as a result of lactose therapy (49). Lactitol (a derivative of lactulose) was also shown to reproduce the PSE therapeutic effect (50). Nevertheless, one can argue that based on the aforementioned microfloral alteration, lactose in LNP subjects promotes a ‘healthier’ flora in cirrhosis, thus satisfying the third criteria of Gibson and Roberfroid.

Beneficial effects to host health
Improvement of hepatic encephalopathy and lactose intolerance (a commonly touted benefit of probiotics in yogurt) are enough to qualify lactose for this section. However, the possible benefits of lactose may be further extended by hypothesizing that the similarity of this natural disaccharide to lactulose may also mimic some of the benefits attributed to the latter. Therefore, the similarity of this natural disaccharide to lactulose may be further extended by hypothesizing that the similarity of this natural disaccharide to lactulose may also mimic some of the benefits attributed to the latter. Lactulose has been shown to impact on infections of the gastrointestinal tract (51-53), it has been shown to affect surrogate fecal markers of carcinogenesis (54) and has even been proposed for prevention of IBD (55). Studies in these areas using lactose have been lagging.

The relevance of redefining lactose as a prebiotic
Lactose seems to fit the definition of Gibson and Roberfroid, and therefore it can be considered a conditional prebiotic in LNP subjects.

RATIONALE FOR REDEFINING LACTOSE
Why in particular is it important to recognize lactose as a conditional prebiotic? Its relevance may be linked with the large number of people with LNP status who still consume some lactose (31, 32, 46). As stated above, both Bifidobacteria and Lactobacillus seem to be quantitatively expanded by lactulose. However, the possible benefits of lactose may be further extended by hypothesizing that the similarity of this natural disaccharide to lactulose may also mimic some of the benefits attributed to the latter. Therefore, the similarity of this natural disaccharide to lactulose may be further extended by hypothesizing that the similarity of this natural disaccharide to lactulose may also mimic some of the benefits attributed to the latter. Lactulose has been shown to impact on infections of the gastrointestinal tract (51-53), it has been shown to affect surrogate fecal markers of carcinogenesis (54) and has even been proposed for prevention of IBD (55). Studies in these areas using lactose have been lagging.
confirmation is required. I recently provided physiological evidence using the adaptation concept to support the notion that IBD may be an endogenous ‘probiotic’ deficient disease (56) and thus support the therapeutic role of exogenous probiotics. It also raises a testable hypothesis regarding early pathogenic events in some lower intestinal diseases. The notion of altered bacterial flora in pseudo membranous colitis and emergence of Clostridium difficile as a cause is now accepted and is largely contributed to by antibiotics (57). In this event, the possible acute loss of protective flora leads to a reasonably clear outcome. However, what if protective bacterial loss occurs for unknown reasons (diet, antibiotics in feeds, food additives, etc.) over several weeks, months or years? In this paradigm IBD could represent disease with intermediate time of loss of endogenous ‘probiotics’ and perhaps colon cancer as a long term consequence. The observed increased risk of cancer in IBD could potentially be facilitated. An obvious question in these scenarios is what role might LNP status play in early pathogenesis. Would lactose consuming LNP subjects be equally at risk as lactose nonconsuming LNP/LP subjects? What is the role of lactase consumption in floral maintenance in LNP populations?

For example, my colleagues and I are currently reassessing results of studies examining the relationship between dairy consumption and colorectal neoplasms (manuscript in preparation). There are conflicting outcomes of meta analyses on this subject (58-60). However, there is a suggestion that if the outcome of studies on the subject are reanalysed, by including the frequency of LNP status in the country of origin, then discrepancies in these meta analyses may be explained. As such future dietary studies on dairy and colorectal neoplasms could incorporate measured LNP status as a variable.

**SUMMARY**

This article summarizes data which then are used to argue that lactose should be considered as a conditional probiotic. It is emphasized that in the context of a probiotic, lactose must naturally exert an effect on lower intestinal microflora. Therefore, the consumption or failure to do so might exert subtle protective or permissive pathogenic influences toward a number of diseases. Therefore, the division of populations along LP/LNP status may offer an opportunity to study disease patterns related to bacterial flora. It is suggested that studying the potential influences of genetic dichotomy of lactase status could be modeled after the Framingham (61,62) or Nurses Health Study (63) in which LP or LNP status is determined at the beginning and participants are periodically evaluated.

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**REFERENCES**


