Redefining the Role of Lactase Enzyme as a Therapeutic Intervention for Infant Colic

Reviewed by:
Dr. Nishant Wadhwa
DNB, MBBS, DCh
Pediatric Gastroenterology, Hepatology and Liver Transplantation
Consultant: Sir Ganga Ram Hospital
New Delhi

Infant colic: An overview

Infant colic (IC) is considered to be a benign condition posing as a major burden to families, health care providers and the overall health system. Colic has been traditionally defined as a condition occurring in an otherwise healthy infant characterized by crying or fussing more than three hours a day and for more than three days a week.[1] Later, IC was classified as a functional gastrointestinal disorder (FGID) characterized by the Rome III, and much later, the Rome IV criteria. According to the Rome III criteria, age of infants with colic range from birth to 4 months and they may present with paroxysmal symptoms of irritability, fussing/crying in the absence of an obvious cause, episodes lasting for three hours a day or more. All symptoms are reported to occur at least three 3 days a week and last for at least a week. On the contrary, the Rome IV criteria for IC states that symptoms start and stop by 5 months of age. There are recurrent and extended periods of crying, fussing or irritability reported by caregivers with no evident cause and which are difficult-to-manage. The differences between Rome III and IV criteria for IC are described in table 1.[2]

Table 1: Differences between Rome III and IV criteria for infant colic

Parameter	Rome III criteria	Rome IV criteria
Age limit	Birth-4 months	5 months
Focuses mainly on	Duration of crying (at least 3 hours/day for at least 3 days/week for at least 1 week)	Crying/fussing which cause distress to parents
Additional criteria	Separate criteria not given	Includes subjective parental reporting of crying more than 3 hours/day for at least 3 days/week and objective record by a 24 hour cry-record diary

Adapted from: Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. *Indian Pediatr.* 2018;55(11):979-987.

Epidemiology

Infant colic is considered to be a common condition prevalent in approximately 20% of the world's population.[2] However, a wide variation has been reported in the prevalence rates according to different studies. A systematic review of literature done in 2001 revealed that occurrence rate of IC in prospective studies varied from 3% to 28% and in retrospective studies between 8% to 40%.[3] Variations in prevalence according to age have also been reported. The prevalence rate of IC in infants younger than 12 months of age has been estimated to range between 2% and 73%.[4] Other variations in prevalence have been reported due to differences in diagnostic criteria. Based on Rome III criteria, two population-based surveys have estimated prevalence rates of IC to be 5.9% and 10.4%, respectively.[5,6] Furthermore, the prevalence of IC may also be influenced by parents' perception of intensity and duration of crying episodes, methods used for collection of data about crying, parents' well-being, and different child rearing practices among communities.[7] Regardless of variations in prevalence, it appears to be one of the most common complaints in the primary health sectors; hence, a complete understanding of the underlying pathophysiology is essential.[1]

Table 2: Factors implicated in the pathophysiology of infant colic

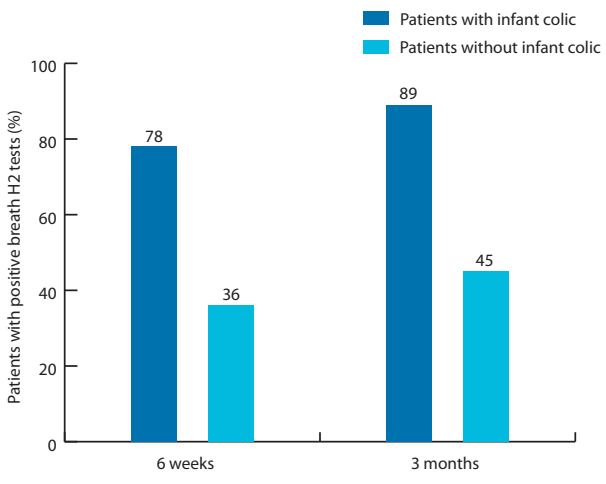
Gastrointestinal	Non-gastrointestinal		
	Maternal	Infantile	Environmental
• Transient lactose intolerance and excessive gas production • Cows' milk protein allergy • Increased motilin hormone levels causing intestinal hyper-peristalsis • Imbalance in intestinal microbiota • Gastroesophageal reflux disease • Barrier alterations • Gastrointestinal inflammation	• Age • Educational background • Smoking • Alcohol consumption • Antenatal maternal stress and anxiety • Poor feeding techniques	• Difficult infant temperament • Inability to maintain normal homeostasis • Immaturity of central nervous system • Early form of migraine	• Lack of family support • Family stress • Behavioral cause such as altered parent-child interaction

Adapted from: Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. *Indian Pediatr.* 2018;55(11):979-987.

Pathophysiological mechanisms

The exact etiology of IC remains elusive; however, several theories have been proposed to explain the factors associated with the condition. Several non-gastrointestinal and gastrointestinal causes have been implicated (Table 2). The non-gastrointestinal theories are broadly categorized as maternal, infantile and environmental factors.[2] Gastrointestinal factors seem to be more important in the pathophysiology of IC ascribed to the fact that the term "colic" implies an abdominal origin. Gastrointestinal mechanisms such as increased intraluminal gas, gut dysmotility and visceral pain have been hypothesized in the occurrence of IC.[1] Other gastrointestinal theories which are thought to contribute to IC pathogenesis include immaturity of enteric nervous system leading to intestinal contraction and colic, increased motilin receptors causing intestinal hyper-peristalsis, cow milk hypersensitivity, intestinal dysbiosis, barrier alterations, and gastrointestinal inflammation.[2,8] Another factor that is posited as an etiological factor in IC is transient lactose intolerance.

Figure 1: Signs of lactose intolerance in patients with infant colic



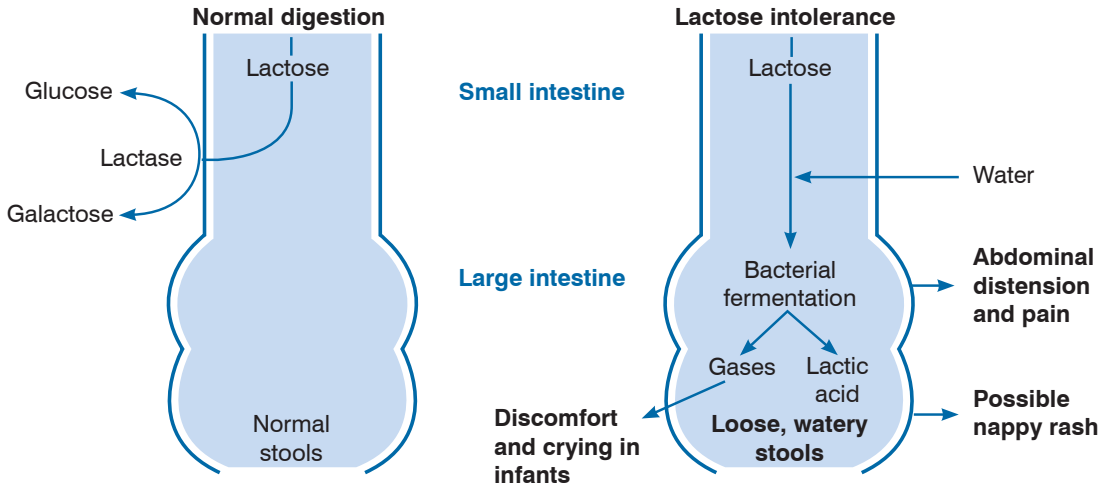
Adapted from: Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J Pediatr.* 1988;113(6):979-84.

Lactose intolerance in infant colic

It has been suggested that transient lactose intolerance attributed to lactase deficiency may contribute to the development of IC in an infant.[9] Moore et al[10] reported that signs of lactose intolerance as depicted by positive breath H2 tests were significantly higher in patients with IC as compared to those without it at 6 weeks (78% vs. 36%) and at 3 months (89% vs. 45%) (Figure 1).

Low levels of lactase results in incomplete digestion of lactose in the small intestine which then reaches the large intestine and is acted upon by colonic microbiota such as lactobacillus and bifidobacterium, thereby leading to its fermentation along with hydrogen and lactic acid production. Increased hydrogen production in the lower bowel causes distension of the colon which results in pain while osmotic pressures generated by lactose and lactic acid in the colon lead to influx of water and cause further distension with acidic diarrhea (Figure 2). Furthermore, the increase in gas production is believed to act as a major source of discomfort in infants; hence giving rise to symptoms of IC.[2,9]

Figure 2: Resultant gastrointestinal symptoms in a child with lactose intolerance



Adapted from: 1) Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. *Indian Pediatr.* 2018;55(11):979-987. 2) Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet.* 2001;14(5):359-63.

Presenting features

Infants with colic present with long periods of crying and hard-to-calm behavior. Parents of such infants are found to be in an anxious and distressed state owing to the fact that the episodes of crying occurs for no apparent reason which start and stop abruptly. They describe that the type of crying associated with colic appear to be more urgent and piercing making them feel that their infant is experiencing grave pain. It is reported that crying is often accompanied with hypertonia, facial flushing, withdrawal of legs towards abdomen and flatulence.[2] Although IC is not associated with dangerous long-term complications, it may increase the number of visits to the clinic along with creating a stressful environment for other family members and deteriorating the infant's quality of life. Few evidences have further suggested that IC may predispose children to develop recurrent abdominal pain, frequent FGIDs, mood disorders and migraine in their later lives. Hence, it is important for healthcare providers to identify the condition and initiate appropriate management for better outcomes.[8]

Management approaches

Both non-pharmacological and pharmacological options have been evaluated for the management of IC. Interventions may be broadly classified into behavioral modifications and parental counseling, pharmacological agents, and dietary interventions.[2]

Behavioral modifications and parental counseling: Parental reassurance/counseling is considered to be one of the mainstays of IC management. It is important to help parents/caregivers cope with their infant's symptoms and to provide support for the infant-family relationship. Certain strategies adopted by the parents/caregivers may help in soothing the infant, including swaddling, shushing, stomach position, swinging, and sucking.[8]

Pharmacological agents: Drugs that have been evaluated in the management of IC include dicyclomine hydrochloride, cimetropium bromide, simethicone, sucrose and herbal medications. These agents are mainly used for pain relief in these infants. Although some agents have been shown to be effective in reducing symptoms of IC, their use is not strongly encouraged due to the associated side-effects.[2]

Dietary interventions: Several dietary interventions have been tried and evaluated for the management of IC. In cases of IC secondary to a cow's milk protein allergy, a maternal hypoallergenic diet for breastfed infants and an extensively hydrolyzed formula for bottle-fed infants may result in resolution of colic.[8] In addition, some probiotic strains have shown to be effective in reducing crying time in breastfed infants with colic.[11] Furthermore, treating the underlying lactose intolerance is considered to be an important therapeutic strategy for the management of IC.

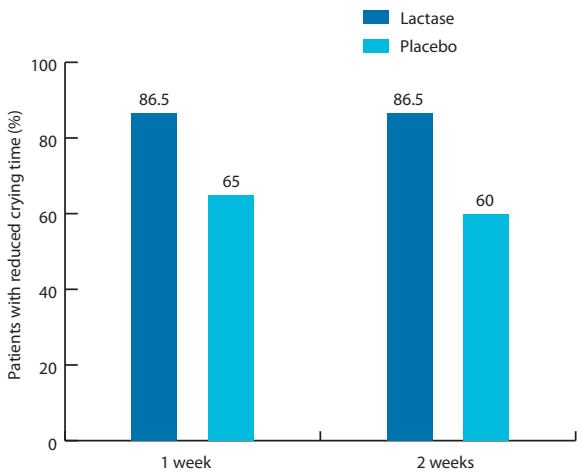
Management of lactose intolerance in infantile colic: Benefits of lactase supplementation

Infants with lactose intolerance may be treated with dietary modifications or lactase supplementation. However, lactose-free formulas have been found to be ineffective in improving symptoms. Moreover, they have the drawback of limiting calcium absorption.[12] On the other hand, lactase supplements have shown to ameliorate gastrointestinal symptoms associated with lactose intolerance.[13] Moreover, it has been suggested that lactase supplementation is beneficial in patients with IC. Hence, it has been recommended that, following exclusion of any organic cause of colic such as esophageal reflux, constipation and infectious intestinal lesions, lactase drops should be used before each feeding in breastfed and formula-fed infants for a week.[14] The clinical benefits of lactase supplementation in infants with colic have been reported in several studies.

- In a recently conducted trial,[15] a total of 104 subjects with IC aged 0-6 months were enrolled and randomized to receive either lactase (n=52) or placebo (n=52). Results showed that a significantly higher percentage of the study participants receiving lactase reported reduction in crying time as compared to those subjected to placebo at the end of 1 (86.5% vs. 65%, p=0.012) and 2 weeks (86.5% vs. 60%, p=0.002) (Figure 3)
- Similar results were obtained in another study[16] wherein lactase and placebo drops were added to milk formulas to assess if this method of reducing lactose intake led to improvement in subjects with IC. A total of 13 infants were recruited in the study and randomly assigned to add either lactase or placebo drops to their formula feeds for 1 week followed by 2 days wash out. In the following week, the addition was changed so that the subjects served as their own control. Outcomes of the study were assessed in terms of crying time that was recorded by their parents. Results showed that lactase reduced crying time in infants by 1.14 hours per day (p=0.019)
- Likewise, Kanabar et al[9] reported that, in patients with IC, crying time was significantly lower in infants receiving lactase as compared to those receiving placebo (520 minutes vs. 872.5 min, p=0.0052). In addition, mean breath hydrogen levels was also significantly lower in the lactase group (6 ppm vs. 9.5 ppm, p=0.0007) (Table 3), thereby suggesting improvement in symptoms of IC and underlying lactose intolerance with lactase supplementation.

Thus, these findings implicate that lactase supplementation may be an effective therapeutic intervention in infants with colic.

Figure 3: Higher number of infant colic patients with reduced crying time following administration of lactase versus placebo



Adapted from: Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical Efficacy of Lactase Enzyme Supplement in Infant Colic: A Randomised Controlled Trial. *J Pak Med Assoc.* 2018;68(12):1744-1747.

Table 3: Effects of lactase supplementation on crying time and breath hydrogen levels in subjects with infant colic

Parameter	Lactase	Placebo	p value
Crying time (minutes)	520	872.5	0.0052
Breath hydrogen levels (ppm)	6	9.5	0.0007

Adapted from: Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet.* 2001;14(5):359-63.

Method of administration of lactase drops

- Each 1 ml preparation contains lactase enzyme 600 FCC units
- Dosage of drops in infants:
  - » Direction I (for breast feed): Add 4 to 5 drops of lactase drops to few ml of expressed breast milk. The foremilk contains most of the lactose. Wait a few minutes, give this mixture to the baby and then breast feed as normal.
  - » Direction II (for formula/ animal's milk feed): Add 4 to 5 drops of lactase drops per 50 ml of infant formula, when it is warm (30C to 40C). Shake the formula and then feed the baby.

Benefits of lactase drops

- Recommended as per international guidelines (NICE guidelines)
- Generally Recommended As Safe (GRAS) – Natural Enzyme Food Supplement (Approved by FSSAI-Food safety and Standard Authority of India and EFSA-European Food Safety Authority)
- Relieves symptoms of infantile colic like excessive crying (by 45%)
- Improves parent & child bonding, parental care and reduces risk of child abuse
- In rotaviral and other GI infections, reduces diarrhea and colicky symptoms (due to transient lactose intolerance), enabling improved nutritional intake
- Easy to use, great tasting natural supplement that promotes mother's milk (and can also be used with formula feeds)
- Lactase is derived from *Aspergillus oryzae.* This source is best and is recommended by all food regulatory bodies, both in India and in international countries (FSSAI in India and EFSA in Europe). In US, regulatory bodies like USFDA recommend this source as GRAS.
- Lactase is a safe and natural way to prevent infant colic and symptoms of lactose intolerance.

Conclusion

Colic is a condition manifested as inconsolable crying episodes in infants and associated with adverse effects such as maternal depression, child abuse and deterioration in the child's quality of life. The exact etiology of IC remains elusive; however, a number of non-gastrointestinal and gastrointestinal factors have been implicated. Transient lactose intolerance has been identified as a possible causative factor in IC. However, restriction of lactose from the infant's diet is not considered to be feasible as it can limit calcium absorption. Lactase supplementation has been considered beneficial for the management of symptoms associated with IC. Moreover, lactase may also be effective for the management of IC as it has been shown to reduce crying time and symptoms of lactose intolerance in colicky infants.

References

1. Sung V. Infantile colic. *Aust Prescr*. 2018;41(4):105–110.
2. Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. *Indian Pediatr.* 2018;55(11):979-987.
3. Lucassen PL, Assendelft WJ, van Eijk JT, et al. Systematic review of the occurrence of infantile colic in the community. *Arch Dis Child.* 2001;84(5):398-403.
4. Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. *J Pediatr Gastroenterol Nutr.* 2015;61(5):531-7.
5. Van Tilburg MA, Hyman PE, Walker L, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J Pediatr.* 2015;166(3):684-9.
6. Chogle A, Velasco-Benitez CA, Koppen IJ, et al. A Population-Based Study on the Epidemiology of Functional Gastrointestinal Disorders in Young Children. *J Pediatr.* 2016;179:139-143.e1.
7. Zeevenhooven J, Koppen IJN, Benninga MA. The New Rome IV Criteria for Functional Gastrointestinal Disorders in Infants and Toddlers. *Pediatr Gastroenterol Hepatol Nutr.* 2017;20(1):1–13.
8. Daelemans S, Peeters L, Hauser B, Vandenplas Y. Recent advances in understanding and managing infantile colic. *F1000Res.* 2018;7:F1000 Faculty Rev-1426.
9. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet.* 2001;14(5):359-63.
10. Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J Pediatr.* 1988;113(6):979-84.
11. Fatheree NY, Liu Y, Taylor CM, et al. Lactobacillus reuteri for Infants with Colic: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *J Pediatr.* 2017;191:170-178.e2.
12. Yuan DT. Management of lactose intolerance in infants. *Am Fam Physician.* 2010;81(8):933; author reply 933-4.
13. Medow MS, Thek KD, Newman LJ, et al. Beta-galactosidase tablets in the treatment of lactose intolerance in pediatrics. *Am J Dis Child.* 1990;144(11):1261-4.
14. Xinias I, Analitis A, Mavroudi A, et al. Innovative Dietary Intervention Answers to Baby Colic. *Pediatr Gastroenterol Hepatol Nutr.* 2017;20(2):100-106.
15. Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical Efficacy of Lactase Enzyme Supplement in Infant Colic: A Randomised Controlled Trial. *J Pak Med Assoc.* 2018;68(12):1744-1747.
16. Kearney PJ, Malone AJ, Hayes T, Cole M, Hyland M. A trial of lactase in the management of infantile colic. *J Hum Nutr Diet.* 1998;11:281–285.