Chronic Diarrhea and Associated Secondary Lactose Intolerance in Children: Appraising Role of Lactase Enzyme Supplementation

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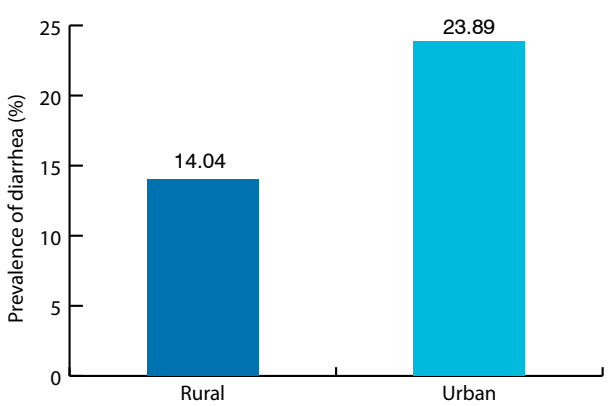
Burden of diarrhea in children: An overview

Diarrheal disease is considered to be a major health problem in children. It contributes to remarkable mortality and morbidity in children under the age of 5 years with the problem being more pronounced in developing countries. It has been estimated that about 2.5 billion cases of childhood diarrhea are reported annually and it accounts for 9% of deaths in under-five children globally. Such data makes diarrhea the second leading cause of death in this population. Furthermore, in South Asian and African countries, about 82% of under-five deaths are caused by diarrhea.[1] Its prevalence in the Indian subcontinent has been estimated to range between 2.2% and 55.6% with children in rural areas less affected as compared to those residing in urban areas (Figure 1).[2] Diarrhea is usually described as an abnormal increase in daily stool fluidity, frequency, and volume from what is considered normal for an individual or more specifically as three or more loose or liquid stools per day due to abnormally high fluid content.[1] However, several forms of diarrhea have been identified based on the duration of symptoms (Box 1).[3]

Figure 1: Indian data representing burden of childhood diarrhea in rural and urban areas



Adapted from: Ganguly E, Sharma PK, Bunker CH. Prevalence and risk factors of diarrhea morbidity among under-five children in India: A systematic review and meta-analysis. *Indian J Child Health (Bhopal)*. 2015;2(4):152–160.

Box 1: Different forms of diarrheal diseases

- Acute diarrhea
- Prolonged diarrhea
- Persistent diarrhea
- Chronic diarrhea
- Post-infectious diarrhea
- Intractable diarrhea
- Congenital diarrhea

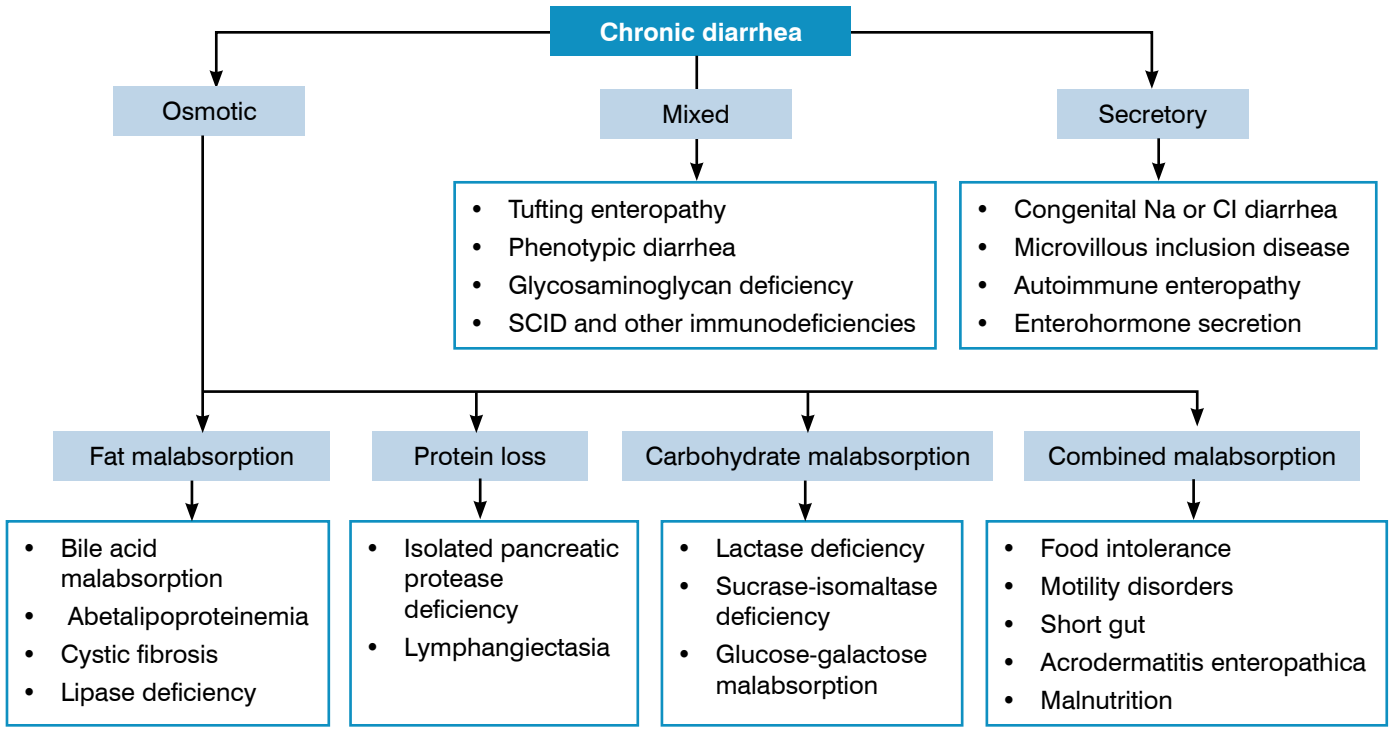
Adapted from: Giannattasio A, Guarino A, Lo Vecchio A. Management of children with prolonged diarrhea. *F1000Res*. 2016;5:F1000 Faculty Rev-206.

Chronic diarrhea in children

Diarrhea is said to be chronic if it persists for more than 4 weeks. It can affect children of any age group, including infants, toddlers, preschool-age children, grade school-age children and adolescents.[4] A global prevalence rate of 3-20% have been reported. The concept of chronic diarrhea is said to differ from that of persistent diarrhea. Major variations between the two are mainly in terms of duration of symptoms and etiology. While persistent diarrhea is an episode of diarrhea with underlying infectious etiology that develops acutely and continues for >14 days, chronic diarrhea lasting for more than 14 days is not only associated with infectious cause but may have other associated causes and malabsorption.[5]

Chronic diarrhea may be caused due to a variety of infectious and non-infectious etiologies. Several etiological classifications of chronic diarrhea have been proposed on the basis of pathophysiology (Figure 2) and presence or

Figure 2: Etiologies associated with chronic diarrhea based on pathophysiology



Adapted from: Lee KS, Kang DS, Yu J, Chang YP, Park WS. How to do in persistent diarrhea of children?: concepts and treatments of chronic diarrhea. *Pediatr Gastroenterol Hepatol Nutr.* 2012;15(4):229–236.

absence of failure to thrive. Enteric infections are regarded to be a major cause of chronic diarrhea in developing and industrialized countries. Furthermore, the enteric infection by common cause in chronic diarrhea have been reported to induce secondary lactase deficiency and resultant lactose intolerance.[5]

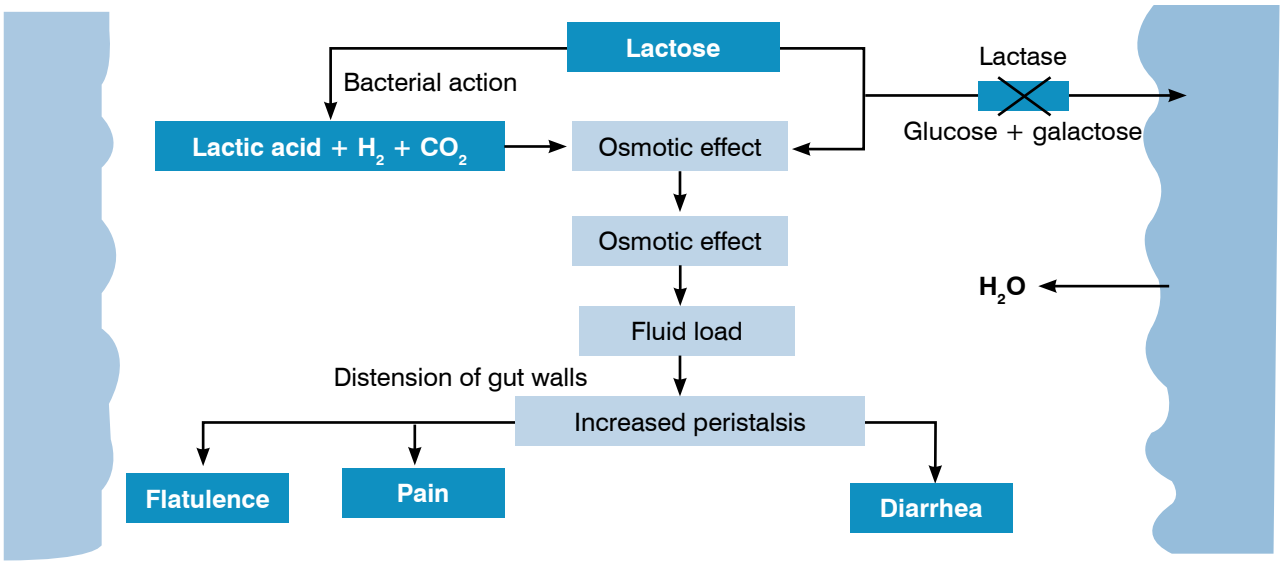
Lactose intolerance secondary to chronic diarrhea

Lactose intolerance has emerged as a common problem in children with diarrhea. It is mainly attributed to the secondary lactase deficiency during diarrhea.[6] Lactase is the enzyme which is responsible for digestion of the disaccharide lactose in the mucosal brush border of the intestine. Reduced levels of lactase in the intestine lead to lactose malabsorption, thus causing its retention in the lumen. Bacteria residing in the colon act upon the unabsorbed lactose and produce gas and short chain fatty acids, thereby resulting in further diarrhea and other associated symptoms (Figure 3). Secondary lactase deficiency is regarded to be a very common condition in children of developing countries due to increased frequency of intestinal infections. Transient lactose intolerance often occurring after episodes of infective diarrhea may be associated with prolongation of the diarrheal disease. Children with secondary lactase deficiency have more pronounced diarrhea as compared to those with primary form and it may also result in further complications in children such as growth retardation and dehydration.[7-9] Furthermore, chronic diarrhea episodes can hamper the physical and psychological aspects of development in children, thus warranting the need of appropriate diagnosis and treatment.[5]

Evaluation of children with chronic diarrhea

History, physical examination and laboratory investigations are regarded to be key elements of the diagnostic approach in children presenting with chronic diarrhea. A detailed medical and family history may aid in determining the cause of diarrhea. Some of the important elements in history include diarrhea duration, frequency, amount of stool passed, appearance of stool and presence of other associated symptoms. Family medical history is recorded to assess if chronic diarrhea and lactose intolerance are familial. Likewise, history related to recent travel, exposure to new water sources and sick contacts may be beneficial. In addition, the child's diet and growth's charts may be evaluated to rule out chronic non-specific diarrhea and other diseases. Furthermore, assessment of red flags is essential to investigate if an organic cause is responsible for the diarrhea episodes (Box 2).[4,5] Laboratory investigations usually include blood tests, stool tests, upper GI endoscopy, and sigmoidoscopy. A hydrogen breath test may also be conducted to evaluate signs of other accompanying

Figure 3: Mechanisms associated with lactose malabsorption



Adapted from: Sibley E. Genetic variation and lactose intolerance: detection methods and clinical implications. *Am J Pharmacogenomics*. 2004;4(4):239-45.

Box 2: Red flags in children with chronic diarrhea

- Stool
  - » Blood
  - » Mucus
  - » Nocturnal
- Weight loss/failure to thrive
- Young age
- Associated symptoms
  - » Fever
  - » Rashes
  - » Arthritis
  - » Perianal lesions

Adapted from: Lee KS, Kang DS, Yu J, Chang YP, Park WS. How to do in persistent diarrhea of children?: concepts and treatments of chronic diarrhea. *Pediatr Gastroenterol Hepatol Nutr.* 2012;15(4):229–236.

conditions such as lactose intolerance.[4] The stepwise approach for evaluating a child with chronic diarrhea is demonstrated in Figure 4. Such an approach may aid in identification of a specific cause, thus guiding appropriate treatment.[5]

Management approaches in chronic diarrhea

It has been suggested that determination of the cause of chronic diarrhea in children is of utmost importance as it is largely responsible for the choice of treatment as well as for predicting good prognosis. Malnutrition is regarded to be an important etiological agent of persisting diarrhea associated with intestinal barrier destruction as well as atrophy of the intestinal villi. Based on underlying cause, treatment options may majorly comprise of general supportive measures, pharmacotherapy and nutritional strategies.[5]

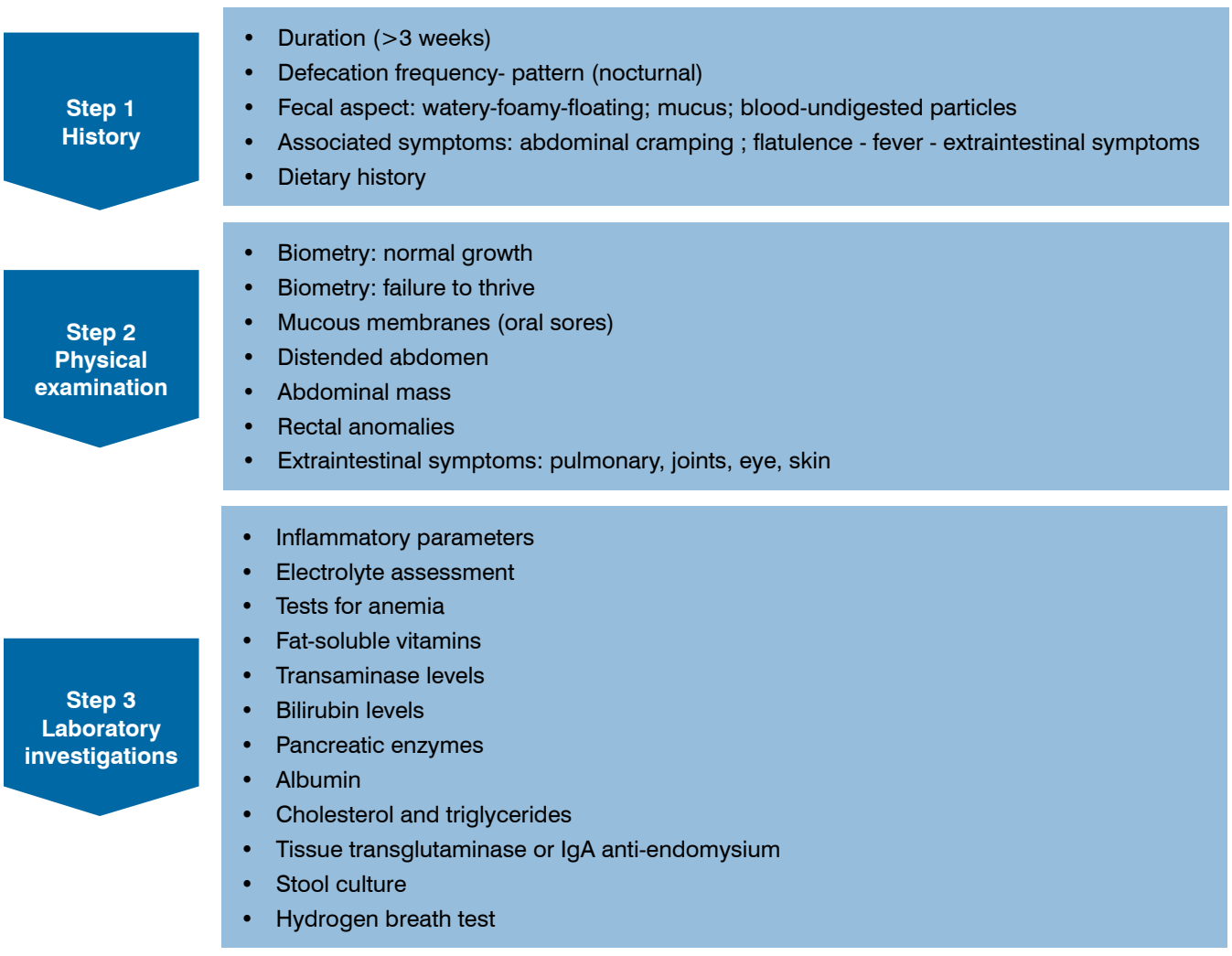
1) General supportive measures

These include steps for the prevention or correction of dehydration. Fluids are indicated with oral rehydration solution (ORS) as the most effective formulation in majority of children with chronic non-severe diarrhea. However, in children with impaired glucose absorption, ORS may lead to worsening of dehydration and diarrhea. These children may require intravenous rehydration until ORS is well-tolerated without aggravation of diarrhea. Another general supportive measure administered in children with chronic diarrhea includes administration of supplementary multivitamins and minerals including zinc.[10] Zinc has been shown to exert beneficial effects such as stimulation of immune response, promotion of ion absorption, and restoration of tight junction and epithelial proliferation.[5]

2) Pharmacotherapy

They include antibiotics for bacterial diarrhea, immune suppressive agents for autoimmune enteropathy, and drugs that can inhibit fluid loss and promote cell growth.[5] Although routine use of antibiotics is not recommended due to their ineffectiveness, they are administered in children with specific non-intestinal or intestinal infections. Correction of these infections is essential for the improvement of chronic diarrhea.[10] Antimicrobials such as metronidazole is administered for Giardia infections while trimethoprim-sulfamethoxazole can be used for Cyclospora and as a second-line antimicrobial for several pathogens.[3] Anti-

Figure 4: Stepwise approach in a child with chronic diarrhea



Adapted from: 1. Chronic diarrhea in children. Available at: https://www.niddk.nih.gov/-/media/Files/Digestive-Diseases/Chronic_Diarrhea_in_Children_508.pdf. Accessed on 3/2/2020. **2.** Lee KS, Kang DS, Yu J, Chang YP, Park WS. How to do in persistent diarrhea of children?: concepts and treatments of chronic diarrhea. *Pediatr Gastroenterol Hepatol Nutr*. 2012;15(4):229–236.

diarrheal agents and anti-emetics are not prescribed to young children with acute or persistent diarrhea as they have no major role in amelioration of dehydration or nutritional status and they may result in dangerous and sometimes lethal side-effects.[10]

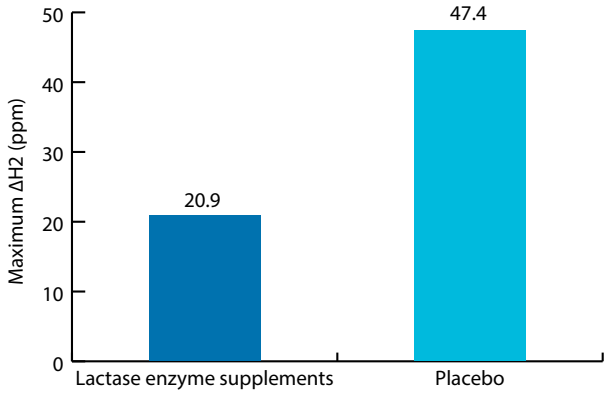
3) Nutritional strategies

Nutritional strategies are considered to be crucial in the management of chronic diarrhea in children as they can break the vicious cycle of chronic diarrhea episodes. These interventions exert general beneficial effects on patients' intestinal function, immune response, and their overall condition. Hence, they are regarded to be one of the major treatment approaches for chronic diarrhea.[5] Probiotics have been shown to be effective in shortening diarrhea duration as well as reducing stool frequency and hospital stay in children with chronic diarrhea, thus appearing as a promising adjunctive therapy in diarrhea management; however, evidences to support their routine use in children with chronic diarrhea are limited.[11]

Management of lactose intolerance secondary to chronic diarrhea

Over time, several alternative dietary therapies have been suggested for the management of primary and secondary lactose intolerance associated with diarrhea. Breast-feeding is usually continued in infants with lactose intolerance and mild diarrheal episodes. Dietary preparations comprising of soy-protein and hydrolysate with specially designed carbohydrate, protein, and fat components have been suggested to be beneficial in managing the diarrheal episodes and secondary lactase deficiency in formula-fed infants.[12] In older children with lactose intolerance, reduced intake of lactose-containing foods is beneficial; however, complete elimination of these products from diet may not be required. Consumption of milk with food and in several

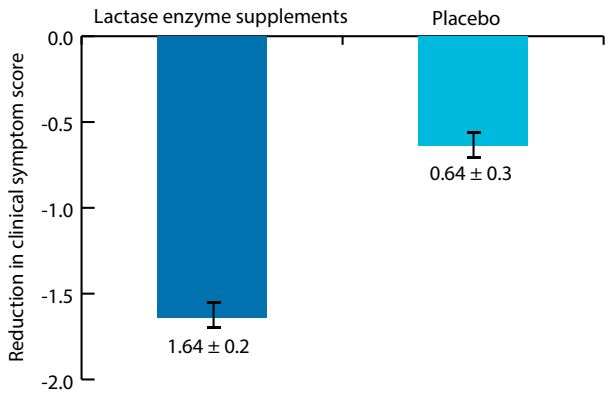
Figure 5: Maximum ΔH2* with lactase enzyme supplements versus placebo in lactose-intolerant children presenting with chronic diarrhea and other gastrointestinal symptoms



*ΔH2, change in breath hydrogen concentration from baseline

Adapted from: Biller JA, King S, Rosenthal A, Grand RJ. Efficacy of lactase-treated milk for lactose-intolerant pediatric patients. *J Pediatr.* 1987;111(1):91-4.

Figure 6: Reduction in clinical symptom score* with lactase enzyme supplements versus placebo in lactose-intolerant children presenting with chronic diarrhea and other gastrointestinal symptoms



*Clinical symptom score was a score generated for each patient to assess symptoms of diarrhea, abdominal pain, gas, bloating, nausea, and vomiting within 24 hours of the breath test

Adapted from: Biller JA, King S, Rosenthal A, Grand RJ. Efficacy of lactase-treated milk for lactose-intolerant pediatric patients. *J Pediatr.* 1987;111(1):91-4.

small portions is advised as doing so improves overall tolerance by slowing the release of lactose in the small intestine.[13] In addition, dietary lactase supplements are suggested for the management of most types of diarrhea with lactase deficiency owing to clinical benefits of the enzyme in controlling intestinal function.[12,14]

Appraising clinical benefits of lactase enzyme supplements

Lactase deficiency represents the main cause of lactose intolerance; hence exogenous lactase supplementation is considered to be a favorable treatment option. Lactase supplements can be administered with milk or as capsules/tablets before consumption of dairy products.[15] In infants, lactase enzyme drops are added to expressed breast milk or the formula some time before feeding.[13] Exogenous lactase is reported to break down lactose into glucose and galactose, thereby allowing an efficient absorption.[16]

Lactase enzyme supplements are available commercially and have been shown to demonstrate good efficacy in pediatric subjects.[15] Oral lactase supplements have been shown to ameliorate the severity of gastrointestinal symptoms after a lactose challenge in children with lactose intolerance.[17,18] In a clinical setting comprising of children presenting with chronic diarrhea and other gastrointestinal symptoms, addition of lactase supplements just before the ingestion of milk has been shown to be effective in decreasing breath hydrogen production (Figure 5). In addition, use of lactase enzyme supplement led to significantly higher reduction in clinical symptom score as compared to placebo in these lactose-intolerant children (1.64±0.2 vs. 0.64±0.3, $p<0.01$) (Figure 6) Furthermore, no side effects attributable to lactase supplements were noted.[19] Thus, lactase enzyme supplements and milk or dairy products treated with lactase enzyme represent an effective and well-tolerated treatment option which allows lactose-intolerant children to consume dairy products freely and reduces the diarrheal episodes without causing adverse effects.[18,19]

Conclusion

Chronic diarrhea in children is a global public health burden with a worldwide prevalence ranging from 3 to 20%. Several etiological agents have been identified which are not associated with only infectious agents but with several other causes and malabsorption. The enteric infection by common cause in chronic diarrhea has been shown to induce secondary lactase deficiency resulting from mucosal injury of small intestine. Management approaches in chronic diarrhea comprise of general supportive care, drug therapies and nutritional therapies. As lactose intolerance is one of the common problems encountered in children with diarrhea, its management is considered largely essential. Lactase enzyme supplements are available commercially and have been shown to demonstrate good efficacy in pediatric subjects with problems of lactose intolerance. Lactase enzyme supplements have been shown to decrease hydrogen breath production as well as clinical symptom scores in children presenting with chronic diarrhea and other gastrointestinal symptoms without causing adverse effects, thus demonstrating their effectiveness and tolerability.

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