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Research

Prevalence of lactose intolerance among children with severe acute malnutrition with diarrhea admitted to the Institute of Child and Mother Health, Bangladesh

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Background
Lactose intolerance (LI) is a common complication of severe acute malnutrition (SAM). However, in low-income countries it is often not possible to determine whether LI is present.

Objective
This study aimed to document the prevalence of LI among SAM cases with diarrhea admitted to the Institute of Child and Mother Health, Bangladesh.

Methods
This cross-sectional study was carried out from July 2022 to June 2023 in all admitted children aged 2 months to 59 months diagnosed as SAM with diarrhea either at presentation or during the disease course. Children having invasive diarrhea, cystic fibrosis, celiac disease, inborn error of metabolism and associated serious comorbidity were excluded, leaving a sample size of 61. Stool reducing substance ⩾1+ by Benedict test and stool PH < 5.5 by pH strip were considered to be a positive test for LI.

Results
The prevalence of LI in our sample was 28%. The predominant age group was 6-23 months (48%); 48% resided in a peri-urban area. Consumption of animal as well as formula milk was a common practice in all age groups. Kwashiorkor (46%) was the commonest malnutrition type with 39% LI association. LI was significantly associated with persistent diarrhea. These patients had a longer hospital stay as well. On logistic analysis, the presence of perianal excoriation, a history of diarrhea in the 2 months prior to hospitalization, and heavy stool frequency in the last 24 hours were found to be significant predictors for LI.

Conclusions
The prevalence of LI in SAM patients was 28%. Persistent diarrhea, the presence of perianal excoriation, diarrhea in the last 2 months, and heavy stool frequency in the last 24 hours were significantly associated with LI.

INTRODUCTION
Malnutrition in children is a major health problem in many developing countries. Annually, it is the cause of eight million cases of under-five mortality globally (National Guideline, 2017). When severe acute malnutrition (SAM) presents with diarrhea, mortality may be higher (Brewster 2006; Talbert et al. 2012). Diarrhea in SAM patients has infectious as well as non-infectious causes (Kvissberg et al. 2015).

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Lactose intolerance is a common complication of diarrhea in these patients (Nyeko et al. 2010). It is an important cause of treatment failure as well. Prevalence of secondary LI among SAM patients is 26-100% in different settings (Nyeko et al. 2010; Khan et al. 2018; Beau et al. 1989; Fagundes-Neto 1985; Fajardo et al. 1979).

Lactose is a disaccharide formed from glucose and galactose linked via a β-1→4 glycosidic bond that is hydrolyzed by β-galactosidase (lactase) (Grenov et al. 2016). Lactase is found in the small intestine, particularly in the jejunum at the tips of villi. Thus, it is more vulnerable to intestinal injury and intestinal diseases than other disaccharidases (Heyman 2006; Vesa et al. 2000). Primary lactase non-persistence is characterized by genetically programmed reduction of lactase activity after weaning (Heyman 2006; Schaafsma 2008). This decline continues from infancy until adolescence to early adulthood (Lomer et al. 2008).

The term 'primary lactose intolerance' was coined to describe the congenital absence of the lactase enzyme (Ali et al. 2021). Secondary lactase deficiency is usually temporary and occurs more often in children than adults (Heyman 2006). Causes include celiac disease, giardiasis, infectious enteritis, mucosal injury, bacterial overgrowth, and drug-induced enteritis (Ali et al. 2021; Wedlake et al. 2008; Ghoshal et al. 2004). A large quantity of lactose consumed in a short period by a lactose malabsorber results in poor hydrolysis of lactose or hampered absorption of it in the small intestine. It proceeds to the large intestine, where it holds or withdraws water to the intestinal lumen. The symptoms in either case then include abdominal pain, diarrhea, nausea, flatulence, bloating, and perianal excoriation (Heyman 2006; Schaafsma 2008; Ali et al. 2021).

SAM patients have a reduced activity of intestinal lactase (Grenov et al. 2016). Feeding these children with a high carbohydrate-containing F-75 diet during the stabilization phase of treatment often results in osmotic diarrhea and sometimes ultimately treatment failure.

There are multiple techniques for assessing lactose malabsorption in malnourished children. A tissue disaccharidase assay obtained from a small intestinal biopsy is considered to be the gold standard. The other widely practiced methods include a blood glucose rise following a carbohydrate (CHO) tolerance test, hydrogen breath test, genetic testing, measurement of fecal markers, and the assessment of metabolic enzymes. Anthropometric markers are sometimes used as part of the assessment. Though stool pH and reducing substance testing have relatively poor sensitivity (9-28%) and only moderately good specificity (74-81%), it is easy, non-invasive, economical, and performed at the bedside (Erickson et al. 2020).

The initial stabilization phase of SAM treatment starts with an F-75 diet that contains high CHO and low sodium, protein, and fat. In the rehabilitation phase, the diet is CHO-depleted and protein and fat-rich, aiming at weight increment. Enteric infection, along with impaired CHO absorption owing to villous blunting, often leads to osmotic diarrhea during the stabilization phase. To address this, a determination of CHO malabsorption is crucial, followed by a modified diet plan.

In Bangladesh, there is currently very limited data on LI in SAM with diarrhea. The current study is designed to document the prevalence of lactose intolerance among children with severe acute malnutrition with diarrhea admitted to the Institute of Child and Mother Health (ICMH), Bangladesh.

MATERIALS AND METHODS

This was a cross-sectional study conducted from July 2022 to June 2023 at the pediatric ward of ICMH, Dhaka. All admitted children aged 2-59 months diagnosed with SAM with diarrhea either at presentation or during their disease course were enrolled in the study. Those having invasive diarrhea, diagnosed cases of cystic fibrosis, celiac disease, inborn errors of metabolism, or associated serious comorbidity were excluded, leaving a final sample of 61 children.

After obtaining informed written consent from the legal guardian, a detailed history of each child was taken, and a thorough physical examination was done, including anthropometry. Stepwise treatment of SAM was started immediately.

As a screening test at our low-resource center, we performed a stool test. A positive LI test was defined as stool pH <5.5 along with the Benedict test measuring the presence of reducing substances (⩾1) in the feces (Kvissberg et al. 2015; Nyeko et al. 2010).

In addition to the Benedict test and stool pH, stool microscopy was performed for fat globules, ova, parasites, pus cells, and cysts. The data were analyzed statistically using SPSS version 22. An ethical clearance certificate was obtained from the Institutional Review Board of ICMH before the study.

RESULTS

As shown in Table 1, 28% of the sample children were lactose intolerant. Although those under six months and those from urban areas appear to have been more affected, these differences were not statistically significant. In Figure 1, the feeding practices of these patients are documented. While breastfeeding was common among those under 24 months of age, exclusive breastfeeding among those under 6 months old was rare.

In this sample of 61, 28 children (46%) were diagnosed with kwashiorkor, 19 (31.1%) with marasmic-kwashiorkor, and 14 (23%) with marasmus. Lactose intolerance was found in 11(39.3%) kwashiorkor, 4 (21%) marasmic-kwashiorkor, and 2(14.3%) marasmus cases. These differences were statistically significant (Table 2).

Most of the participants presented or developed diarrhea of a duration of 14 days or less (44; 72.1%) while the rest (17; 27.9%) had a duration of diarrhea of >14 days. Among those with a duration of diarrhea ⩽14 days, there were 5 (11.3%) with lactose intolerance, and among those with a duration of >14 days, there were 12 (70.6%) with lactose intolerance. These findings were statistically significant (Table 3).

Among the children who were lactose tolerant, 42 had a hospital stay of 10 days or less, one stayed 11 to 13 days, and one stayed 14 days or more. While those having lactose intolerance had a hospital stay of 14 days or more in 11 cases, 11 to 13 days in 5 cases, and 10 days or less in a single case (Figure 2).

On logistic analysis, the presence of perianal excoriation (p=0.04), diarrhea in the last 2 months (p=0.01), duration of diarrhea ⩾14 days (p <0.001), and heavy stool frequency in the last 24 hours (p=0.01) were significantly associated factors in LI (Table 4).

Table 1. Characteristics of the sample SAM patients (n=61)

Characteristics	Lactose tolerant (44)	Lactose intolerant (17)	p-value
Age			
<6 months	11 (57.9)	8 (42.1)	0.246
6-23 months	23 (79.3)	6 (20.7)	
24-59 months	10 (76.9)	3 (23.1)	
Sex			
Male	23 (71.8)	9 (28.2)	0.963
Female	11 (72.4)	8 (27.6)	
Residence			
Urban	15 (83.3)	3 (16.7)	0.415
Peri-urban	19 (65.5)	10 (34.5)	
Rural	10 (71.4)	4 (28.6)	

p-value <0.05 was significant

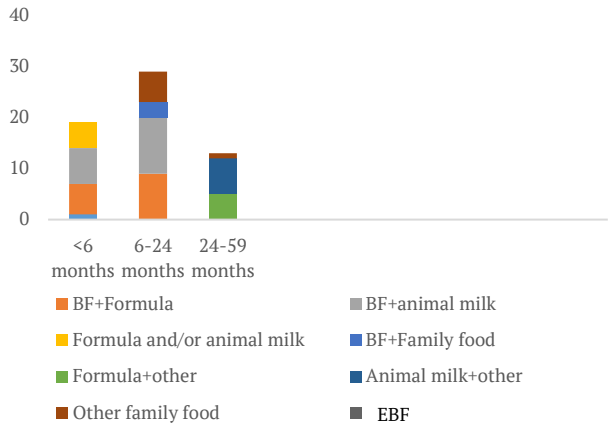

Figure 1. Feeding practices by age among SAM patients
BF=breastfeeding

Table 2. Lactose tolerance by type of malnutrition

Type of malnutrition	Lactose tolerant n=44	Lactose intolerant n=17	95% CI	p-value
Kwashiorkor (28)				
Present	17	11	0.107-1.10	0.067
Absent	27	6		
Marasmic-kwashiorkor (19)				
Present	15	4	0.466-6.06	0.425
Absent	29	13		
Marasmus (14)				
Present	12	2	0.558-14.2	0.197
Absent	32	15		

p-value <0.05 was significant

Table 3. Lactose tolerance in SAM patients by duration of diarrhea

Duration of diarrhea	Lactose tolerant n=44	Lactose intolerant n=17	OR	95% CI	p-value
14 days or less	39	5			
>14 days	5	12	18.7	4.6-75.78	<0.001*

p-value <0.05 was significant

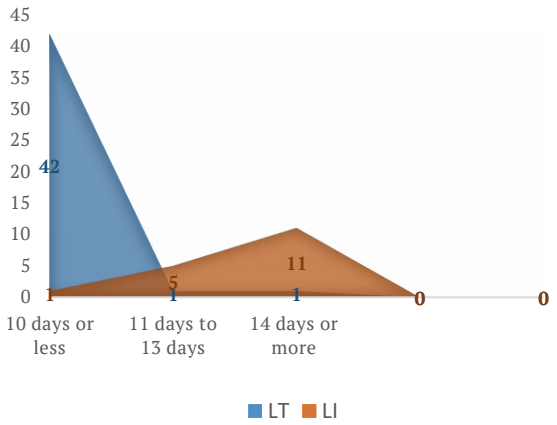

Figure 2. Lactose tolerance and duration of hospital stay (p-value: <0.001)
LT = lactose tolerance; LI= lactose intolerance

Table 4. Logistic analysis examining factors associated with lactose intolerance in SAM patients

Factors	Lactose intolerant N (%)	Unadjusted OR	95% CI	p-value
Edema				
Present	14 (29.8%)	1.56	(0.37-6.44)	0.54
Absent	3 (21.4%)			
Vomiting				
Present	11 (26.2%)	0.77	(0.23-2.52)	0.66
Absent	6 (31.6%)			
Perianal excoriation				
Present	11 (73.3)	18.3	(4.38-76.60)	0.04
Absent	6 (13%)			
Diarrhea in the last 2 months				
Present	14 (73.7%)	36.4	(7.67-172.55)	0.01
Absent	3 (7.1%)			
Stool frequency in the last 24 hours				
Heavy	12 (48%)	5.72	(1.67-19.54)	0.01
Not heavy	5 (13.9%)			

DISCUSSION

The estimated prevalence of LI in this current study was found to be 28% which was close to a previous study carried out by Nyeko et al. (2010). In their study among 196 severely malnourished children with diarrhea aged 3-60 months, the prevalence of LI was 25.5%. Moreover, they used the same technique to diagnose LI, i.e., stool reducing substance and pH measurement (Nyeko et al. 2010). A lower prevalence of LI (18.3%) was found by Gebremariam et al. (2020), who also used the same method. In another study, Kanth et al. (2019) used a hydrogen breath test to detect LI, and they found a 31% prevalence of LI.

While in our study, children aged 2 months to 59 months were enrolled, Nyeko et al. (2010) included children from 3 to 60 months, Gebremariam B. et al. (2020) studied children under 5 years, and Ali et al. (2021) selected children from 3 months to 2 years. Kanth et al. (2019) included a much older group, children from 5 to 15 years old. We found LI most prevalent in children below 6 months, though Nyeko et al. (2010) did not divide the infantile age group and found the

highest prevalence of LI in the below 12 months group. They observed a decreasing trend of LI with the advancement of age, much similar to the current study. Ali et al. (2021) documented that the 3-12 months age group was most vulnerable to LI, and Gebremariam et al. (2020), the <12 months group.

We included 32 males and 19 females in this study, with a male-female ratio of 1.6:1, while among LI patients the ratio was 1.1:1. The proportionate number of male and female participants was almost equal in most of the studies, e.g., 1.17:1 in the study by Nyeko et al. (2010), 1.14:1 by Gebremariam et al. (2020), and 0.99:1 by Ali et al. (2021). Kanth et al. (2019) found a 1.94:1 male-female ratio, unlike the mentioned studies. The area of residence was not taken into account by the mentioned studies. The location of our study institute could be the reason behind the peri-urban majority of the participants.

Nyeko et al. (2010) found that a duration of EBF ⩾4 months was a significant negative factor for the onset of LI. Gebremariam et al. (2020) found that cow milk (P=0.008) and therapeutic milk formula (P=0.004) were significantly related to LI. We did not attempt to link feeding practices with LI; rather only documented age-wise feeding practices of the participants.

Most of the participants of our study had kwashiorkor, followed by marasmic-kwashiorkor and marasmus. We did not find any significant correlation between any of these three varieties of malnutrition and LI. Nyeko et al. (2010) documented a predominance of marasmus, followed by kwashiorkor. They found a significant positive association between kwashiorkor and LI, as well as a negative association between marasmus and LI.

Similar to the study by Nyeko et al. (2010), we took the duration of diarrhea into account and found a statistically significant association between persistent diarrhea (i.e., diarrhea of 14 days or more) and LI. In addition to this finding, we also counted the hospital stay of the children and observed a longer hospital stay in those having LI. This observation reflects the possible complications and morbidity of LI in association with SAM as elucidated by several researchers (Kvissberg et al. 2015; Maitland et al. 2006; Talbert et al. 2012).

On logistic analysis, we found that the presence of perianal excoriation, diarrhea in the last 2 months, and heavy stool frequency in the last 24 hours were significant factors associated with LI. On similar analysis, Nyeko et al. (2010) documented diarrhea in the previous 3 months, edematous malnutrition, perianal excoriation, and frequency of stool in the past 24 hours to be significant factors. In comparison, Gebremariam et al. (2020) found problems after taking milk, the type of therapeutic milk formula, and high stool frequency in the past 24 hours to be significant predisposing factors.

LIMITATIONS

Our sample size was relatively small. The test that we used lacks sensitivity and has only moderate specificity. Further research comprising larger samples with more diagnostic techniques is recommended.

CONCLUSION

The prevalence of lactose intolerance in the current study of SAM patients was 28%. It was significantly associated with persistent diarrhea, the presence of perianal excoriation, diarrhea in the last 2 months, and heavy stool frequency in the last 24 hours.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, software, format analysis & visualization: MAA, AR; Data curation: MAA, MAR, BH; Investigation: MAA, BH, HA, ASB, AH; Project administration, supervision, validation, resource & funding: MAA; Writing (draft & review): All authors read the final version and consent for the publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN SCIENTIFIC WRITING

Nothing to disclose.

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