Breath hydrogen excretion in normal newborn infants in response to usual feeding patterns: Evidence for "functional lactase insufficiency" beyond the first month of life

Sequential studies of morning breath hydrogen excretion were carried out in the homes of 16 normal breast-fed or formula-fed infants during the first 5 months of life. Except for two infants whose stools did not produce H_2, all infants had elevated breath H_2 excretion (>10 parts per million) during and after the first month of life. There was a significant relationship to age ($P < 0.005$) for all three measures of H_2 excretion (4-hour average, peak, and preprandial), with mean values being highest in month 2, elevated but lower in month 1, and dropping significantly in months 3 and after. Additional 24-hour studies with six 7-week-old infants demonstrated that H_2 excretion was inversely related to state of arousal, more likely to be detected in the afternoon, and not clearly related to time of feeding. These findings suggest that incomplete lactose absorption in response to usual feeding patterns persists beyond the first months of life in all infants. The pattern of breath H_2 excretion indicates a probable developmental change in quantity and consistency of carbohydrate substrate delivered to colonic flora. Although elevated breath H_2 excretion in response to normal feeding demonstrates incomplete absorption, it should not be used to determine an infant's status as a "lactose malabsorber."
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INCOMPLETE ABSORPTION OF LACTOSE in normal infants in response to usual feeding patterns (functional lactase insufficiency) is a common phenomenon in the first week of life.[1-4] Persistence of this phenomenon up to 1 month of age has been suggested in studies of small intestinal disaccharidase activities,[5] stool reducing sugars or acidity,[6] and breath H_2 excretion[3] in at least some infants. However, evidence is insufficient to determine whether incomplete lactose absorption occurs in some or all infants, and whether it persists beyond the first month of life. We used the technique of breath H_2 testing for incomplete carbohydrate absorption in a longitudinal study of normal breast-fed or formula-fed term infants to obtain repeated measures of the presence or absence of carbohydrate absorption for up to 5 months. Similarly, changes in breath H_2 excretion over 24 hours were monitored to determine the normal excretion pattern of H_2 and therefore the likelihood of detecting incomplete lactose absorption at different times during the day.

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METHODS

In the longitudinal study, 16 normal infants with uncomplicated prenatal and perinatal histories were recruited from general pediatric practices soon after birth. After informed parental consent, infants were studied during the morning hours (9:30 AM to 1:30 PM), beginning at 12 to 44 (mean 22) days of age at approximately 2-week intervals for four to 10 (mean 6.5) home visits (total 104). Of the 16 infants, six were breast-fed only (<1 bottle/day),

four formula-fed only, and six breast-fed infants began formula-feeding between 5 and 15 (mean 10) weeks of age. No solid foods were introduced before 3 months of age, and small amounts of cereal were started in only two formula-fed infants by this time. Parents were asked to feed their infants as usual, and no attempt was made to structure the timing, frequency, or method of parental feeding practice. In the 24-hour studies, two infants from the longitudinal study and four additional normal infants were observed under similar conditions in their homes at 6 to 8 weeks of age. Four infants were exclusively breast-fed, and two were exclusively formula-fed.

To permit breath samples to be obtained in a manner that was both acceptable to the infant's parents and did not interfere with the state of the infant, a modification of the nasal prong technique as described by Perman et al.[7] was used. In this modification, a nasal cuff of soft rubber is chosen, large enough to slightly distend the anterior nares when in place. The infant rapidly becomes accustomed to placement of the nasal cuff, and with a little practice, one can easily place it in the nares of sleeping infants without waking them. A small-diameter (2 mm OD) silicone cannula is then placed within the nasal cuff. Absence of contact with the nasal mucosa permits uninterrupted sampling while the cuff is in place. Small aliquots of expired air are drawn into the syringe during expiration in synchrony with the infant's breathing pattern until a 30 ml sample is obtained. The method is very acceptable to parents and permits repeated sampling over 24 hours independent of the state of the infant.

During home visits, samples were obtained regularly at 30-minute intervals except during feeding, providing three to nine (mean six) samples per visit in the longitudinal studies, and 42 to 47 (mean 44) samples in the 24-hour studies. Time and state of the infant (cry/fuss, awake and content, sleeping) were recorded for each sample. In addition to breath samples, a behavioral log of state, feeding times, and occurrence of bowel movements was completed by the research assistant.

Birth weights of all infants were obtained, and during the longitudinal study each infant was weighed at least twice (average three times) with the same portable scales (Seco Model 235410, Germany). Birth weights of the study infants were between the 25th and 95th percentiles and were maintained without significant percentile change throughout the study in all but three infants; weight decreased from the 95th to the 75th percentile in two, and from the 90th to the 50th percentile in one, without clinical symptoms.

Samples were analyzed within 24 hours by gas chromatography using a microthermistor detector (Carle Instruments, Anaheim, CA). Columns were arranged to permit initial detection of H_2 from a 3 ml sample. While the remainder of this sample was backflushed, CO_2 concentration was determined from a second 1 ml sample automatically applied to parallel columns and detected by the microthermistor. Columns and detector were kept at 50° C, with nitrogen used as carrier gas (50 ml/min). Concentrations were obtained by comparisons of peak heights with known standards (Canox, Oakville, Ont., Canada) run daily. The system can measure 55 parts per million (ppm) H_2 and 5% CO_2 with relative standard deviations of <1%; minimum concentration of <5 ppm H_2 is reliably detectable. Hydrogen concentration was normalized to alveolar CO_2 concentration as described by Niu et al.[8] to reduce variability related to sample collection. Samples with CO_2 <20% predicted alveolar concentration were discarded as technically insufficient. Normalized H_2 values >10 ppm were taken as indicating incomplete lactose absorption.[9,10] In six infants, fresh stool samples were tested in vitro for capacity to produce H_2 from lactose according to the method of Levitt et al.[11]

In the longitudinal study, three H_2 excretion measures were calculated for each infant for each visit: (1) 4-hour average, representing the arithmetic mean of all values taken during the home visit; (2) peak, representing the highest value obtained; and (3) preprandial, representing the last H_2 value(s) taken within 30 minutes prior to feeding. Because values followed a log normal distribution, calculation of mean values across infants and tests of significance used H_2 measures after log transformation. Results are presented as mean ± 1 SD after antilog conversion to illustrate the variation to be expected in measured H_2 values. To determine whether values from one visit were independent of those from succeeding visits, intraclass correlation coefficients (R_I) were calculated on random pairs of visits during the second month for each infant. For 4-hour average, peak, and preprandial measures, R_Is were low (0.23, 0.27, 0.26, respectively) indicating that values from one visit were poor predictors of values during subsequent visits. Consequently, values obtained at each visit were treated as independent points for subsequent analyses.

To determine patterns of change in H_2 excretion over time, a one-way analysis of variance against time for visits in months 1, 2, 3, and 4 or after was performed, with subsequent Tukey post hoc tests used to determine location of significant differences. To determine the effect of state, a one-way ANOVA against state was performed for all samples taken during the 24-hour studies, with post hoc tests when indicated. For this comparison, states included crying/fussing, awake and happy, short-duration sleep (60 minutes or less), and long-duration sleep (more than 60 minutes).

RESULTS

Longitudinal studies. In response to usual feeding situations, end-expiratory H_2 excretion was highly variable and persisted beyond the first month of life. In two infants, no H_2 excretion was detected during any home visits (n = 7 and 5 visits, respectively) between the ages of 2 and 12 weeks. When fresh stool samples from these infants were tested, no change in H_2 concentration was detected during in vitro stool testing in response to added lactose, compared with control tubes to which no lactose was added, suggesting that these infants lacked sufficient numbers of the bacteria necessary to produce an H_2 signal. In four H_2-excreting infants, increased H_2 was produced with the addition of lactose to stool in vitro.

In the other 14 infants, H_2 excretion for each measure was highest during the second month of life (4-hour average 27 ppm; peak 47 ppm; preprandial 19 ppm) and was significantly related to age ($P < 0.005$) (Fig. 1). Significant differences were found between the first 2 months and months 3 and 4 ($P < 0.05$). Mean values fell below 10 ppm by month 3 for both 4-hour average and preprandial measures, and below 15 ppm for peak values, but individual elevated H_2 values continued to be found during subsequent weeks in many infants.

In the first 2 months, the prevalence of visits during which positive values for average, peak, and preprandial measures were obtained was 73%, 89%, and 73%, respectively. In later months, the prevalence of positive values declined, but elevated values were still detected in 43%, 62%, and 38% of visits, respectively. These figures could be expected to be lower if fewer samples were taken per visit.

To prevent misinterpretation resulting from averaging effect, individual responses were considered. There were no apparent differences in pattern or amount of H_2 excreted among infants breast-fed, formula-fed, or both breast- and formula-fed. Persistent elevated H_2 excretion was demonstrated in all infants. Four-hour average and preprandial H_2 values exceeded 20 ppm on at least one visit after the first month of age in all but one infant, in whom peak H_2 excretion was 28, 17, and 17 ppm at 3, 5, and 7 weeks, respectively, and <10 ppm at the following visits. In the group as a whole, individual patterns of H_2 excretion at consecutive visits were highly variable and precluded the use of findings from any one visit to define H_2 excretion status. Thus, although the pattern of H_2 excretion of most infants was characteristic of the average values for the group (Fig. 2, subject 1), in others a visit with no H_2 excretion could be preceded and followed by visits with elevated values (Fig. 2, subject 2). Only two infants showed a progressive decline in H_2 excretion levels in subsequent visits (Fig. 2, subject 3).

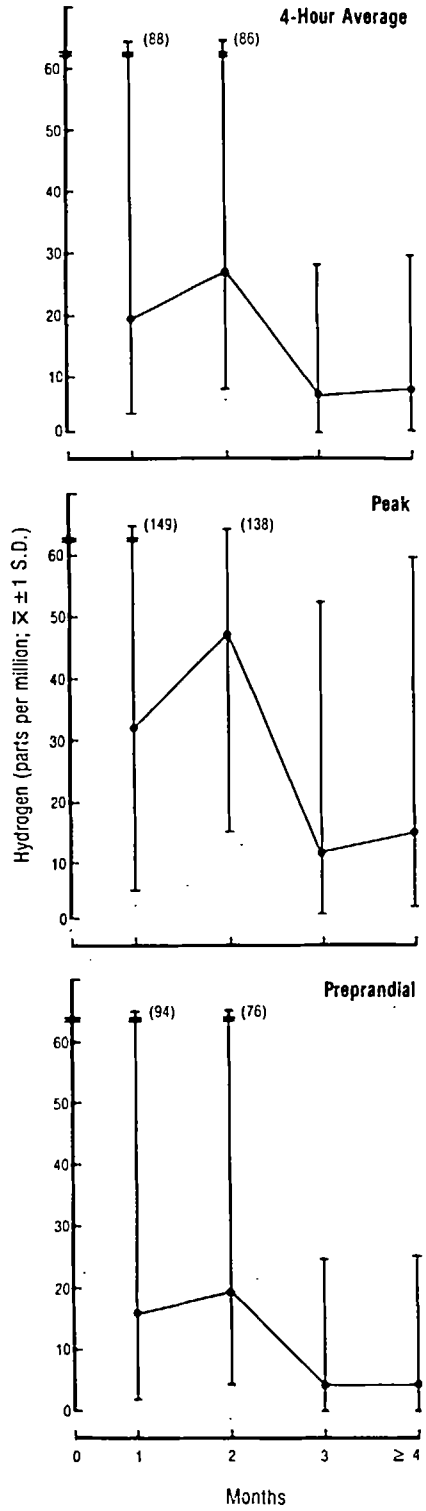

Fig. 1. Pattern of H_2 excretion related to month of sampling for 4-hour average, peak, and preprandial measures. Means and standard deviation are shown after antilog conversion from log-transformed H_2 values used for calculation to illustrate variability of values obtained.

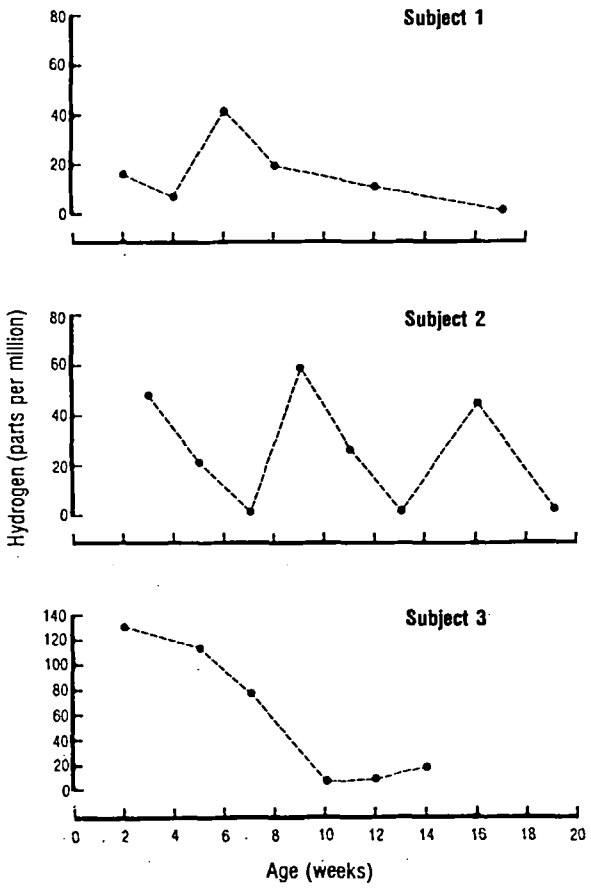

Fig. 2. Individual patterns of H_2 excretion on consecutive visits. Each point represents H_2 values based on average H_2 excretion (ppm) over 4-hour home visit. *Subject 1* represents curvilinear pattern typical of the group as a whole; *subject 2* represents variable pattern; *subject 3* illustrates progressive roughly linear decline in H_2 excretion, seen in only two infants.

Twenty-four-hour studies. Despite considerable intra- and intersubject variation, elevated H_2 values occurred most of the day in all infants. Positive values were most likely to occur during the afternoon (noon to 6:00 PM), and least likely during the morning (6:00 AM to noon) (Fig. 3). In this unstructured feeding situation, there was no discernible relationship with feeding times. Although H_2 values often rose steadily during prolonged sleep, this was not invariably true. There was, however, a significant overall relationship to state ($F[3,262] = 10.18$; $P < 0.001$), such that level of H_2 excreted was inversely related to state of arousal (Table). Thus, values obtained during cry/fuss were lowest, and those obtained during prolonged sleep were highest; values during awake and content, and short-term sleep were intermediate. Finally, dramatic decreases in H_2 values were often apparent after a bowel movement. In all subjects in the longitudinal and 24-hour studies, breath H_2 values declined in all of 10 occurrences when bowel movements followed an elevated value (mean decrease 68%).

Table. Relationship of state to breath H_2 excretion values over 24 hr in six infants

	Observations	*H_2 (ppm) ($\bar{X} \pm SD$)*
1. Crying/fussing	32	18 ± 4
2. Awake and content	64	38 ± 4
3. Short-term sleep (≦60 minutes)	46	52 ± 7
4. Long-term sleep (>60 minutes)	124	67 ± 5

Significance: One-way ANOVA: ($F[3,262] = 10.18$; $P < 0.001$. Comparisons significant at $P < 0.05$ by post hoc Tukey test: 2 and 3 vs 1 and 4; 1 and 2 vs 3 and 4.

DISCUSSION

Although lactose is usually the sole carbohydrate nutrient during the first few weeks of life, little is known about its absorption in response to typical feeding patterns. The technique of analysis of expired breath for H_2 concentration is an indirect but potentially useful method for the assessment of carbohydrate absorption in infants, primarily because it is relatively noninvasive and permits repeated sampling over time. Our findings with this technique have implications for understanding the functional capacity of the small intestine to handle the carbohydrate loads presented to it, factors affecting breath H_2 excretion, and some important constraints on the interpretation of elevated H_2 levels in infants.

Previous studies have suggested the possibility of a transient period of incomplete lactose absorption in the early postnatal weeks. Studies by Auriccio et al.[5] subsequently replicated by Antonowicz et al.,[12] demonstrated that small intestinal lactase activity reaches adult levels at birth in full-term infants and persists until the second year of age. Assuming maximum velocity of lactose hydrolysis, Auricchio et al. estimated that full-term newborn infants could hydrolyze approximately 60 gm/24 hr of lactose, and speculated that the lactose load ingested by breast-fed infants exceeds the ability of the small intestine to hydrolyze the sugar.[5] However, measurement of lactase activity and estimations of total small intestinal lactase probably overestimate the capacity of the small intestine to handle lactose loads, because actual hydrolysis and absorption depend on a variety of other factors, including feeding pattern, rate of gastric emptying, transit, motility, streaming of intestinal contents, presence of the unstirred layer, and product inhibition.[13] Consequently, although lactase activity reaches its highest levels at birth, it does not follow that lactose absorption by the small intestine will be complete, or that available lactase is sufficient to hydro-

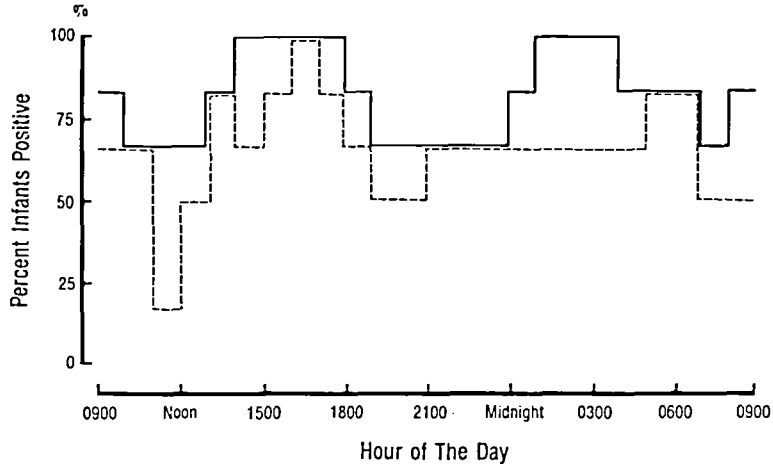

Fig. 3. Percent of infants with positive evidence of incomplete lactose absorption by elevated breath H_2 excretion at different times of day. H_2 excretion: —— ≥10 ppm H_2; --- ≥20 ppm H_2.

lyze either the quantity or the distribution of the lactose load from the usual feeding patterns in the early postnewborn period.

Apparent confirmation of incomplete lactose absorption in the newborn period has been documented in at least some infants by measurement of stool reducing sugars and acidity.[6, 14, 15] Incomplete sugar absorption appears to persist at least until 1 month of age in some infants, as measured by these techniques.[6] However, colonic bacterial metabolism of carbohydrates incompletely absorbed by the small intestine tends to remove evidence of reducing sugars in the stool.[2, 16, 17] Similarly, acidity in the cecum following incomplete carbohydrate absorption is higher than rectal acidity,[18] and thus stool acidity is only very indirect evidence of incomplete carbohydrate absorption. Consequently, absence of reducing substances or acidity cannot be taken as evidence of complete absorption by the small intestine.

In normal adults, the presence of hydrogen gas in expired breath occurs only as a result of colonic bacterial fermentation,[19, 20] because sufficient numbers of lactose-fermenting bacteria are limited to the colon. Assuming the same for infants,[21] detection of the presence or absence of H_2 excretion in expired breath provides more direct evidence of incomplete small intestinal carbohydrate absorption than lactase assays or stool studies. The main finding in our study is the persistence of elevated breath H_2 excretion beyond the first month of life in response to usual feeding patterns in all infants tested who were capable of H_2 production. Absence of H_2 excretion in two infants most likely resulted from the absence of intracolonic H_2-producing bacteria, as previously reported in adults.[22] Evidence for incomplete lactose absorption by breath H_2 excretion has been reported previously for hospitalized premature infants up to 7 weeks[4, 23] and for hospitalized term infants in the first week of life.[1-4] MacLean and Fink[23] reported that all premature infants excreted elevated H_2 levels by the third week of life and that H_2 values tended to increase in postnatal life. Our findings in term infants indicate that the trend to increasing elevation and frequency of positive breath H_2 values continues until the second postnatal month but decreases thereafter. In addition, although elevated breath hydrogen values are the rule rather than the exception in the first 2 months, the pattern of elevated H_2 excretion subsequently becomes increasingly intermittent. These patterns suggest that, in the early postnatal period, colonic bacteria are almost constantly exposed to incompletely absorbed lactose but that this exposure becomes intermittent as the infants grow older. This evolving functional sufficiency may reflect some combination of increasing total lactase activity in the small intestine related to normal growth in size and length, changes in quantity of lactose ingested, or changes in frequency and regularity of feeding.

Previous authors have reported a semiquantitative dose-response relationship between carbohydrate reaching the colon and volume of H_2 excreted in response to fasting conditions, in both adults and toddlers.[24, 25] Consequently, the progressive increase and subsequent decrease over time of average H_2 concentrations might indicate an increase and decrease in quantity of incompletely absorbed substrate. However, the quantity of intracolonic gas produced and its excretion via the lungs are subject to a variety of factors other than the quantity of lactose incompletely absorbed, and may also be expected to change as the infants grow older. Changes in nonsubstrate factors such as colonic pH,[26] type and number of colonic bacteria,[27] gut perfusion,[28] and, as in our study, intestinal gas content

(recency of bowel movement) have all been demonstrated to affect H_2 excretion rates. In particular, because colonic acidity tends to attenuate H_2 production[26] and is more common in the early postnatal period,[6, 14, 29] the measured H_2 concentration may underestimate the quantity of incompletely absorbed carbohydrate in the first months of life or explain the relatively lower concentrations obtained in the first compared with second months of life. Similarly, changes in H_2 excretion rates might equally represent changes in quantity or type of colonic bacteria.[27] Although bacterial populations tend to remain stable in the absence of diet changes,[29, 30] preliminary evidence from CH_4-excreting infants suggests that the composition of gut flora may be quite sensitive to short-term changes in carbohydrate absorption related to feeding.[31]

Our data support the concept that incomplete lactose absorption in the early newborn period should be understood as functional (or physiologic) lactase insufficiency rather than lactose malabsorption. The use of morning test periods in most previous studies of lactose absorption in neonates[3, 23] has probably resulted in underestimation of both the prevalence and magnitude of incomplete absorption. It is unlikely, therefore, that incomplete lactose absorption is indicative of "malabsorption." This interpretation is consistent with the lack of negative effect on growth and the absence of clinical symptoms.[2, 4, 6, 14] In addition, the incompletely absorbed lactose is probably recovered through colonic bacterial production and subsequent absorption of short-chain fatty acids[16, 32] and may play a role in establishing appropriate colonic flora.[29, 33]

During a typical feeding, infants tend to ingest a lactose dose very similar to the challenge of a standard tolerance test (2 gm/kg).[2, 23] However, the H_2 response to normal feeding situations differs from that of the lactose breath hydrogen test,[9, 34, 35] both in lacking a reproducible temporal relationship to lactose ingestion and in not being predictive of lactose absorption on subsequent days. These differences may be related to the absence of fasting conditions or less structured feeding schedules in the home compared with the hospital setting, although a similar lack of relationship with lactose ingestion has been reported in hospitalized premature and term infants.[2, 4, 23] Indeed, development of a breath test to determine "lactose malabsorption" in individual infants may be hampered both by short-term[4] and long-term variability in breath H_2 excretion patterns. The range of variability in H_2 responses makes it unlikely that incomplete lactose absorption that is physiologic will be distinguishable from that which is abnormal on the basis of height of H_2 rise. In part, short-term variability is significantly related to behavioral state and bowel movements, factors that are more difficult to control in infants than in older children and adults. The relationship of H_2 excretion to degree of arousal noted in our 7-week-old infants was reported not to occur in premature infants[23] but is similar to that reported for toddlers.[25] This difference may be related to the relative absence of prolonged sleep episodes in premature infants, compared with older infants and toddlers,[36] and the increasing H_2 levels associated with prolonged as compared with short-term sleep demonstrated in our study. In addition, prevalence of incomplete absorption varies according to the time of day of testing and the outcome measure used (for example, average or peak hydrogen). The relative increase of H_2 excretion in the afternoon has also been seen in normal adults ingesting regular diets,[10] although, not surprisingly, this pattern is much exaggerated in our 7-week-old infants fed lactose. Thus, a standard lactose breath hydrogen test is unlikely to be helpful as a predictor of abnormal lactase activity or lactose absorption in this age group.

In summary, the pattern of breath H_2 excretion in early postnatal life suggests that incomplete lactose absorption continues to occur in response to typical feeding patterns well beyond the first month in all normal infants. Age-related changes in the concentration of H_2 excreted imply developmental changes, either in the balance between carbohydrate ingestion and the capacity of the small intestine to handle lactose loads, or in nonsubstrate factors affecting the H_2 signal, or both. Elevated breath H_2 levels detected in response to typical feeding patterns should not be interpreted analogously to elevated breath H_2 excretion in response to lactose loads in fasting older children and adults. Efforts at developing an infant breath H_2 test for purposes of differentiating normal from abnormal small intestinal lactase activity will have to control for factors affecting both short-term and long-term variability in H_2 excretion, including age, time of day, behavioral state, and intestinal gas content at time of testing.

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