J Pediatr (Rio J). 2018;94(5):455–457

Jornal de Pediatria
www.jped.com.br

EDITORIAL

New insights into the fecal microbiota of children living in a slum: association with small bowel bacterial overgrowth☆,☆☆

Novas ideias sobre a microbiota fecal de crianças que vivem em uma favela: associação com supercrescimento bacteriano do intestino delgado

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The study by Mello et al. from the group of Dr. Mauro Batista de Morais provides additional information on the impact of living in a slum on small bowel bacterial overgrowth (SIBO), as well as some nutritional and anthropometric parameters, and adds new data on the fecal microbiota composition.[1] Using real time-PCR technique, the authors compared the composition of the fecal microbiota of children with or without SIBO and presence of stunting and hemoglobin status and anemia. At total of 100 children, aged between 5 and 11 years, who lived in a slum in the outskirts of São Paulo, Brazil, were studied. SIBO was diagnosed by means of a hydrogen (H_2) and methane (CH_4) breath test (BT) following the ingestion of 10 g lactulose. Results showed that 61% of the children studied had a BT compatible with SIBO and a lower mean height/age-score ([-0.48 ± 0.90] *vs.* [-0.11 ± 0.97]; $p = 0.027$), as well as capillary hemoglobin ([12.61 ± 1.03 g/dL] *vs.* [13.44 ± 1.19 g/dL]; $p < 0.001$). Children with SIBO presented a higher frequency of *Salmonella* spp. when compared to those without SIBO (37.7% *vs.* 10.3%; $p = 0.002$). Higher counts of total *Eubacteria* ($p = 0.014$) and *Firmicutes* ($p = 0.038$) were observed in children without SIBO, while a higher count of *Salmonella* ($p = 0.002$) was found in those with SIBO.

Firstly, the authors need to be commended in their efforts, as engaging the participants and their families in collecting breath and stools samples must not have been an easy task. Their experience with previous studies made them request the help of a community leader to secure successful completion with a large number of subjects.

SIBO is defined as an increase in the number of endogenous symbiotic bacteria in the small bowel and can be an asymptomatic illness or present from mild and nonspecific intestinal symptoms to a severe malabsorptive syndrome.[2]

DOI of original article:
https://doi.org/10.1016/j.jped.2017.09.003

☆ Please cite this article as: Lifschitz C, Sieczkowska A. New insights into the fecal microbiota of children living in a slum: association with small bowel bacterial overgrowth. J Pediatr (Rio J). 2018;94:455–7.

☆☆ See paper by Mello et al. in pages 483–90.

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https://doi.org/10.1016/j.jped.2017.12.002

As a consequence of SIBO, children may suffer from nutritional deficiencies, weight loss, and growth stunting. The development of non-invasive and widely available BTs, a renewed interest in investigating SIBO has been observed, demonstrating that this condition is more prevalent than previously thought and that it may be an under-recognized cause of pediatric morbidity. Studies show that SIBO is not limited to children with structural gut abnormalities or functional and motility gastrointestinal disorders, but that it also affects those living in unsanitary conditions or treated with proton pump inhibitors (PPI).[3–6] Bacteria responsible for SIBO are mostly Gram-negative, with lipopolysaccharide (LPS) in their cell membranes. LPS participates in triggering local inflammatory processes, leading to mucosal lesions that result in increased intestinal permeability of macromolecules, and consequent malabsorption syndrome and high nutrient fermentation in the colon and this can result in higher H_2 production, as observed in the study by Mello et al.[1]

Although BTs are important for the diagnosis of carbohydrate maldigestion syndromes and SIBO, standardization is lacking regarding indications for testing, test methodology, and interpretation of results. Recently, results of a consensus meeting of experts to develop guidelines for clinicians and research for adult testing were published.[7] For diagnosis of SIBO lactulose or glucose have been used; the consensus doses were 10 and 75 g, respectively. In addition, BTs are useful for diagnosis of CH_4-associated constipation and evaluation of bloating/gas but are not for the assessment of oro-cecal transit. It was agreed that an increase in H_2 by $\geq$20 ppm over 90 min during a glucose or lactulose BT for SIBO is considered positive, while CH_4 levels $\geq$ 10 ppm are considered positive. The diagnosis of SIBO is based on the appearance of a H_2 peak in breath before the colonic peak. The reason why BTs are not useful in measuring oro-cecal transit time is the great inter- and intraindividual variability. A study in adults showed that the mean and standard deviation of mouth to cecum transit time was 68 ± 24 min in non-CH_4 producers and significantly longer in CH_4 producers (111 ± 52 min [$p < 0.005$]).[8] From Fig. 2 of such article it can be calculated that the mouth to cecum transit time was as low as approximately 45 min in two subjects and under 75 min in 20 of the 65 subjects studied, regardless of their CH_4-producing status. In such subjects, a H_2 peak at 60 min would be wrongly interpreted as compatible with SIBO. To complicate the interpretation of BT results even further, no such consensus exists for children. Small bowel length ranges between 90 and 100 cm in children aged 3–7 year, and 120–160 cm in those aged 8 years to early teens.[9] It is not known whether the oro-cecal transit time will be comparable in children with both extremes of bowel length (90 and 160 cm). Therefore, when using 60 min as the cutoff point of H_2 elevation for diagnosis of SIBO, as Mello et al. did, there is the potential risk of overdiagnosing SIBO in those with rapid oro-cecal transit time. Moreover, early validation studies in adults performed with doses of lactulose ranging from 5 to 40 g demonstrated that oro-cecal transit times are shorter with increasing doses of lactulose.[9–11] A 5-year-old could weigh around 14 kg (less if stunted), making the dose of lactulose received 0.7 g/kg. As in the study[1] the same dose was given to all subjects, an 11-year-old weighting 35 kg would have received 0.3 g/kg of lactulose. The impact of the doses on transit time is unknown in children, but it could be hypothesized that, in younger children, a higher dose per kilogram of body weight could lead to a more rapid transit time and, again, an overdiagnosis of SIBO. In adults, comparison studies of lactulose H_2 BT and scintigraphy performed simultaneously have shown a strong correlation ($r = 0.945$, $p < 0.01$).[12] Although there is no reason to suspect that such correlation would not exist in children, such studies have not been performed, mostly for ethical reasons.

Regardless of the issues described above, the authors did observe stunting and lower hemoglobin levels in the group in whom SIBO was diagnosed, supporting their diagnostic criteria. The study was unable to determine whether these findings were the consequence of malabsorption from SIBO, poor nutrient intake, losses and wastage from repeated illnesses, and/or diarrhea, or a combination of those factors. The other gas measured in the study was CH4. Methanogenic archaea are among the anaerobic microorganisms present in the human microbiota and produce CH_4 by metabolizing H_2 and CO_2.[13] The most prevalent methanogenic archaea in humans is *Methanobrevibacter smithii*, which can constitute up to 10% of the anaerobes of the intestinal microbiota. Studies have associated breath CH_4 excretion with diverticulosis, irritable bowel syndrome, colorectal cancer, and chronic constipation with retentive fecal incontinence. We found that the prevalence of SIBO was significantly higher in children who received PPI for three months, when compared with controls as determined by H_2 and CH_4 excretion.[5] Although no significant differences were observed in CH_4 excretion between groups, 19.4% of those in the PPI group and 12.9% of those in the control group would have had a false-negative result had CH_4 not been taken into account.

Finally, it was observed that children with SIBO presented a higher frequency of *Salmonella* spp. compared to those without SIBO, while higher counts of total *Eubacteria* and *Firmicutes* were demonstrated in children without SIBO. These findings are in contrast with the authors' previous study comparing microbiota of children from different socioeconomic levels living in the same urban area.[14] In that study, higher counts of total *Eubacteria*, *Firmicutes*, and *Bacteroidetes phyla* organisms, *Escherichia coli*, *Lactobacillus* spp., and *M. smithii* were found in the children living in poverty, whereas higher counts of *Salmonella* spp., *Clostridium difficile*, and *Clostridium perfringens* were observed in the children living in satisfactory housing conditions ($p < 0.05$). It is obvious that many factors influence microbiota composition, not all of which are known at this time.

There is considerable inter-individual diversity in the actual composition of the microbiota and changes in microbial composition occur with age, with a high level of variability at the two ends of life (childhood and old age).[15] For example, one of the controllable environmental factors that influence the composition of the host microbiome is the diet; the high-fat, sugar-rich Western diet contributes to a *Bacteroides*-dominated microbiome, while with a high-fiber diet contribute to a microbiome dominated by *Firmicutes*, with a strong correlation between long-term diet and enterotypes.[16] Regarding ecological succession, the *Bifidobacterium*-dominated microbiota of the child changes over time into the *Bacteroidetes*- and *Firmicutes*-dominated microbiota of the adult,[17] remaining fairly stable through adulthood in the absence of disturbances

such as long-term dietary changes or repeated antibiotic intervention.

In conclusion, the present study adds another important layer to understand the complexity of normal and abnormal intestinal microbiota as it is affected by environmental conditions and, in turn, how it affects human health.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Mello CS, Rodrigues MS, Filho HB, Melli LC, Tahan S, Pignatari AC, et al. Fecal microbiota analysis of children with small intestinal bacterial overgrowth among residents of an urban slum in Brazil. J Pediatr (Rio J). 2018;94:483–90.
2. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology. 2006;130:S78–90.
3. dos Reis JC, de Morais MB, Oliva CA, Fagundes-Neto U. Breath hydrogen test in the diagnosis of environmental enteropathy in children living in an urban slum. Dig Dis Sci. 2007;52:1253–8.
4. Hegar B, Hutapea E, Advani N, Vandenplas Y. A double-blind placebo controlled randomized trial on probiotics in small bowel bacterial overgrowth in children treated with omeprazole. J Pediatr (Rio J). 2013;89:381–7.
5. Sieczkowska A, Landowski P, Kaminska B, Lifschitz C. Small bowel bacterial overgrowth associated with persistence of abdominal symptoms in children treated with proton pump inhibitors. J Pediatr. 2015;166:1310–2.
6. Sieczkowska A, Landowski P, Zagozdzon P, Kaminska B, Lifschitz C. Small bowel bacterial overgrowth in children: a comprehensive review. J Pediatr Gastroenterol Nutr. 2016;62:196–207.
7. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. Am J Gastroenterol. 2017;112:775–84.
8. Cloarec D, Bornet F, Gouilloud S, Barry JL, Salim B, Galmiche JP. Breath Hydrogen response to lactulose in healthy subjects: relationship to methane producing status. Gut. 1990;31:300–4.
9. Reiquam CW, Allen RP, Akers DR. Normal and abnormal small bowel lengths: an analysis of 389 autopsy cases in infants and children. Am J Dis Child. 1965;109:447–51.
10. Bond JH, Levitt MP. Investigation of small bowel transit time in man utilizing pulmonary hydrogen measurements. J Lab Clin Med. 1975;85:546–55.
11. Read NW, Miles CA, Fisher D, Holgate AM, Kime ND, Mitchell MA, et al. Transit of a meal through the stomach, small intestine, and colon in normal subjects and its role in the pathogenesis of diarrhea. Gastroenterology. 1980;79:1276–82.
12. Yu D, Cheeseman F, Vanner S. Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS. Gut. 2011;60:334–40.
13. Balch WE, Fox GE, Magrum LJ, Woese CR, Wolfe RS. Methanogens: reevaluation of a unique biological group. Microbiol Rev. 1979;43:260–96.
14. Mello CS, Rodrigues MS, Araújo-Filho HB, Melli LC, Tahan S, Pignatari AC, et al. Gut microbiota differences in children from distinct socioeconomic levels living in the same urban area in Brazil. J Pediatr Gastroenterol Nutr. 2016;63:460–5.
15. O'Toole PW, Claesson MJ. Gut microbiota: changes throughout the lifespan from infancy to elderly. Int Dairy J. 2010;20:281–91.
16. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334:105–8.
17. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? Front Cell Infect Microbiol. 2012;2:104.