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.\textsuperscript{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\textsubscript{2}) and methane (CH\textsubscript{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]; \textit{p} = 0.027), as well as capillary hemoglobin ([12.61 ± 1.03 g/dL] vs. [13.44 ± 1.19 g/dL]; \textit{p} < 0.001). Children with SIBO presented a higher frequency of \textit{Salmonella} spp. when compared to those without SIBO (37.7% vs. 10.3%; \textit{p} = 0.002). Higher counts of total \textit{Eubacteria} (\textit{p} = 0.014) and \textit{Firmicutes} (\textit{p} = 0.038) were observed in children without SIBO, while a higher count of \textit{Salmonella} (\textit{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.\textsuperscript{2}

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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).\textsuperscript{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.\textsuperscript{7}

Although BTs are important for the diagnosis of carbohydrate malabsorption 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.\textsuperscript{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 \( >20 \text{ ppm} \) over 90 min during a glucose or lactulose BT for SIBO is considered positive, while \( CH_4 \) levels \( >10 \text{ ppm} \) 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 \( 68 \pm 24 \text{ min} \) in non-\( CH_4 \) producers and significantly longer in \( CH_4 \) producers (111 \pm 52 min \( p < 0.005 \)).\textsuperscript{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.\textsuperscript{7} 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.\textsuperscript{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\textsuperscript{7} 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 \( r = 0.945, \ p < 0.01 \).\textsuperscript{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 \( CH_4 \). Methanogenic archaea are among the anaerobic microorganisms present in the human microbiota and produce \( CH_4 \) by metabolizing \( H_2 \) and \( CO_2 \).\textsuperscript{13} The most prevalent methanogenic archaea in humans is \textit{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.\textsuperscript{15} 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 \textit{Salmonella} spp. compared to those without SIBO, while higher counts of total \textit{Eubacteria} and \textit{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.\textsuperscript{14} In that study, higher counts of total \textit{Eubacteria}, \textit{Firmicutes}, and \textit{Bacteroidetes phyla} organisms, \textit{Escherichia coli}, \textit{Lactobacillus} spp., and \textit{M. smithii} were found in the children living in poverty, whereas higher counts of \textit{Salmonella} spp., \textit{Clostridium difficile}, and \textit{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).\textsuperscript{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 \textit{Bacteroides}-dominated microbiome, while with a high-fiber diet contribute to a microbiome dominated by \textit{Firmicutes}, with a strong correlation between long-term diet and enterotypes.\textsuperscript{16} Regarding ecological succession, the \textit{Bifidobacterium}-dominated microbiota of the child changes over time into the \textit{Bacteroidetes}- and \textit{Firmicutes}-dominated microbiota of the adult,\textsuperscript{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