INVITED COMMENTARY

Investigating Probiotics in the Management of Childhood Functional Constipation: A Never-Ending Story?

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Over the past two decades, several studies have evaluated the effectiveness of probiotics in the management of childhood functional constipation (FC). A recently published systematic review by the Cochrane Collaboration concluded that there is still insufficient evidence to draw conclusions as to whether probiotics are effective in improving defecation parameters such as defecation frequency and stool consistency or achieving global treatment success [1]. Despite inconclusive results from studies thus far, researchers have continued their search to find a probiotic strain or a combination of probiotic strains that positively affect childhood FC. In this issue of the journal, Lojanatorn, et al. [2] report the results of a pilot randomized controlled trial evaluating the effect of four weeks of once daily administration of *B.clausii* as single treatment in children (1-5 years of age) with FC according to the Rome IV criteria. The primary outcome was treatment success, defined as 'at least three defecations per week and a stool consistency on the Bristol stool chart of at least three.' Treatment success did not differ between both groups after two and four weeks, nor did defecation frequency, stool consistency or other parameters related to defecation. Thus, they concluded that the probiotic strain *B.clausii* was not more effective than placebo in the treatment of childhood FC after two and four weeks of treatment [2].

To support their hypothesis of the influence of the gut microbiota in childhood FC, Lojanatorn, et al. [2] referred to a previous study in adults with FC [3]. That study showed that the prevalence of methanogenic gut flora was higher in adults with slow transit constipation compared to FC with normal colonic transit times and controls, and did not differ between patients with FC with normal colonic transit times and controls. In addition, patients with FC (both slow transit and normal transit) produced significantly more methane following a carbohydrate challenge compared to controls. Patients with slow transit constipation showed higher methane production compared to patients with FC with normal colonic transit times [3]. Although Attaluri, et al. [3] demonstrated an association between methanogenic flora and colonic transit, the authors could not provide evidence for a causative role. In contrast, these findings may even result from slower gastrointestinal transit times, rather than suggest a causative role of methanogenic flora in the development of FC, as was pointed out by the authors of the original study [3]. In addition, these findings do not implicate that the particular probiotic strain *B.clausii* would be helpful in managing FC. More importantly, the study by Attaluri, et al. [3] was conducted in adults and does not provide evidence that gut dysbiosis plays a role in the pathogenesis of childhood FC nor that probiotics would be effective in the management of childhood FC.

Studies evaluating gut microbiota composition in children with FC have resulted in inconsistent findings and no FC-specific gut microbiota signature has been identified for this patient group yet [4]. The discrepancy in findings on microbiota composition may be contributed by different factors, including differences in study design, such as sample collection and storage, applied analytical techniques, and lack of standardization [5]. Moreover, in children, both the pathogenesis of FC and the development of the gut microbiota during the first years of life differ to a great extent from the situation in adults and consequently, results from adult studies are not necessarily applicable to the pediatric population. Whether the gut microbiota plays a role in the pathogenesis of childhood FC and, if so, in what manner, still needs to be elucidated.

In the study by Lojanatorn, et al. [2], the choice for *B.clausii* seems to be based on the concept that most *Bacillus* spp. can produce lactic and short-chain fatty acids from carbohydrate fermentation, resulting in a lower pH within the colonic lumen, which would theoretically increase peristalsis. However, no studies in the pediatric

population have shown an effect of *B.clausii* on transit times or stool composition thus far. On the contrary, a recent study investigating the application of *B.clausii* in children (6-17 years) with irritable bowel syndrome reported no differences in defecation frequency, nor a softening effect on stool consistency compared to placebo [6]. Lack of identification of microbial signatures linked to childhood FC, including their role in the pathogenesis, limits the evidence-based application of microbiota-based interventions, including probiotics, in children with FC. Therefore, the theoretical basis on which the interventional study by Lojanatorn, et al. [2] is based, including the selection of *B.clausii*, seems thin. Unfortunately, the authors did not longitudinally analyze the composition of the gut microbiota, before and after treatment. In addition, no other microbiota-derived out-come measures, such as stool pH or methane production, were taken into account. This impairs the evaluation of the hypotheses on which the choice for *B.clausii* and the selected dosing regimen were based.

In general, it could be questioned if administration of a single probiotic strain can influence the gut microbiota in a sufficient manner to influence defecation patterns. If the gut microbiota would play a role in childhood FC, then a more impactful manipulation of the gut microbiota might be needed, for instance through the administration of probiotic or synbiotic mixtures or even fecal microbiota transplants (FMT) [7,8]. However, before children are exposed to invasive experimental treatments such as FMT, a better understanding of the role of the gut microbiota in the development of childhood FC is essential. Also, the hypotheses on which such treatment strategies are based need to be tested and well-established in the pediatric population first.

In conclusion, a deeper understanding of the potential role of gut microbiota in the pathophysiology of childhood FC needs to be acquired first, in order to allow the design of future RCTs. In such trials, the choice for probiotics or other microbiota-based interventions, including the dosing regimens, needs to be based on evidence that is relevant to the studied population.

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