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REVIEW PAPER

Proton pump inhibitors – their possible influence on the development of small intestine bacterial overgrowth in children

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ABSTRACT

Proton pump inhibitors (PPIs) are safe drugs that have been commonly used for many years by both general practitioners and specialists. They are widely used in the paediatric population, mainly in the treatment of gastroesophageal reflux disease, but also for oesophagitis, gastritis and/or duodenitis. Proton pump inhibitors use increases the pH of the stomach, which disrupts the physiological defensive barrier and may lead to the development of an abnormal microbiome in the further parts of the digestive tract, resulting in small intestinal bacterial overgrowth (SIBO) and symptoms such as diarrhoea, production of gas, nonspecific abdominal pain, flatulence, lack of growth or weight loss, protein or energy malnutrition, and vitamin A, D, K and B12 deficiency. The study analyses the influence of combining PPIs with probiotics or prokinetics on the chance of SIBO developing in children. There are currently no diagnostic standards or therapeutic guidelines for children diagnosed with SIBO.

KEY WORDS:

children, proton pump inhibitors, small intestinal bacterial overgrowth, gut microbiome, small intestine bacterial overgrowth.

INTRODUCTION

Proton pump inhibitors (PPIs) have been recommended for many years, both by general practitioners and by gastroenterologists and other specialists. They tend be more widely used in primary health care: a study of the safety and side effects associated with PPIs in the period 2008–2011 identified 10,457 recommendations by primary care physicians, but only 6,181 by specialists [1].

These drugs are generally safe, and various preparations are available at smaller doses without prescription: currently 11 omeprazole medications can be bought over the counter in Poland at doses of 10 and 20 mg. Proton pump inhibitors have a wide range of indicated uses, with omeprazole, esomeprazole (after one year of age), pantoprazole and dexlansoprazole (after 12 years of age) being recommended in the paediatric population; however, rabeprazole and lansoprazole are not approved.

Studies performed over 10 years have confirmed the safety of PPIs in children [2]. They are most commonly prescribed for treating gastroesophageal reflux disease (GERD), with or without inflammation of the oesophagus [1, 3–5]. The guidelines of the North American and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition list no indicators for invasive diagnostics in children presenting with clear symptoms of reflux before starting PPIs, unless "red flag" symptoms are observed, or if oesophagitis or other symptoms requiring endoscopy

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of the upper gastrointestinal tract are suspected. It is recommended that PPIs should initially be applied for four to eight weeks in children, excluding infants. If improvement is seen, the course should be continued for another four to eight weeks, while if no improvement is observed, it is suggested that the child should be referred to the gastroenterology department. Proton pump inhibitor treatment should last 12 weeks, and the drug should be taken once daily, 30 minutes before breakfast. All PPIs appear to demonstrate the same level of effectiveness. Additional prokinetic drugs are not recommended [4, 6].

Despite its wide application and safety, PPIs therapy may be accompanied by various side effects, such as headache, constipation, nausea, diarrhoea (including *Clostridioides difficile* infection), respiratory tract infection, vitamin B_{12} deficiency, hypomagnesaemia, pathological bone fracture and small intestinal bacterial overgrowth (SIBO). These have been estimated to occur in 14% of cases [5, 7–9], while an analysis of the Dutch PHARMO Database Network found that approximately 2% of children receiving PPIs were hospitalised with side effects [1]. De Bruyne *et al*. propose that PPIs should be limited to infants and children with GERD or bleeding from the gastrointestinal tract, particularly from the stomach, and recommend that caregivers and patients be informed about their possible adverse effects [5].

Proton pump inhibitors reduce basal and stimulated gastric secretion and inhibit daily gastric acidity, which has a therapeutic effect in conditions such as GERD. However, the resulting increase in pH disturbs the physiological protective barrier, which may lead to the multiplication of an abnormal microbiome in the later sections of the gastrointestinal tract [7, 10–14].

FACTORS INFLUENCING THE GASTROINTESTINAL MICROBIOME

During birth, and immediately afterwards, the digestive tract is colonized with a microbiome. Its composition is influenced by many factors, including type of delivery, the composition of the intestinal flora and genital tract of the mother, feeding method (breastfeeding/formula milk), as well as the stage of maturity of the newborn and the use of antibiotics [7, 15]. Maintaining the homeostasis of the microbiome ensures the correct functioning of physiological mechanisms such as gastrointestinal peristalsis, the levels of bile acids, gastric acid and pancreatic enzymes, and the functioning of the ileocecal valve in later years.

The microbiome of the intestines plays a key role in maintaining the homeostasis of the organism as a whole through complex pathomechanisms influencing the production of vitamins and short-chain fatty acids, regulation of lipid metabolism and gene expression, maintenance of the mucosal barrier, and the functioning of the immune and neurogenic systems. In the intestines, and especially in the colon, the microbiome is abundant and varied, with the number of species ranging from 400 to 1500. Any pathological changes in the composition or functioning of the microbiome may contribute to the development of civilization diseases such as allergies, functional disorders of the digestive tract and inflammatory bowel disease [7, 13, 15–17].

Under physiological conditions, the numbers of bacteria in the stomach and the upper third of the small intestine are typically quite low, i.e. approximately 10^3 CFU/ml, with the most common genera being *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Lactobacillus* and *Corynebacterium*. Bacterial density increases in the lower parts of the gastrointestinal tract, with the highest numbers occurring behind the ileocecal valve (10^9–10^{11} CFU/ml) with the dominance of anaerobic bacteria such as *Bifidobacterium* and *Bacteroides*, as well as *Enterobacteriaceae*, *Klebsiella* and *Eubacterium* [7, 15].

Any disturbance of this balance in the small intestine, and the development of an abnormal microbiome, may have significant effects on health, both in the form of clinical symptoms (diarrhoea, flatulence, non-specific abdominal pain, increased gas emission, skin changes, oedema) and quantitative deficiencies (loss/lack of weight gain, protein and/or energy malnutrition) as well as qualitative (vitamin A, D, K, B_{12} deficiency) and growth disorders, anaemia, osteoporosis or polyneuropathy [7, 10–16, 18, 19]. In addition, erythema nodosum, arthritis, visual disturbances and skin trophic changes have also been observed as a consequence of intestinal dysbiosis [15].

BACTERIAL OVERGROWTH IN THE SMALL INTESTINE IN CHILDREN – A DEFINITION?

Currently, there are no unambiguous criteria for the diagnosis and management of SIBO in children. In physiological conditions, the density of the microbiome present in the stomach and the initial segment of the small intestine is estimated at 10^1–10^3 CFU/ml, as grown from gastroscopic aspirate. To qualify as SIBO, quantitative and/or qualitative abnormalities must be present in the microbiome of the small intestine, accompanied by clinical symptoms.

In earlier years, SIBO was defined as the presence of $\geq 10^5$ CFU/ml bacteria in small intestine aspirate [13, 18, 19]. Patients with values between the physiological and pathological thresholds are not included in the definition. According to the North American consensus on breathing tests, the suggested that the threshold for the diagnosis of SIBO using microbial culture of small intestine aspirate should be 10^3 CFU/ml [9]; this has been confirmed recently [14, 15, 20].

The subject of bacterial overgrowth of the small intestine in children is still a little known topic and the publications are scarce: since 2000, only 149 reports on this subject have been published [7]. This could indicate that

existing knowledge of SIBO is insufficient and its prevalence is underestimated.

SMALL INTESTINAL BACTERIAL OVERGROWTH – DIAGNOSTIC PROBLEMS AND EVALUATION OF PREVALENCE

Two methods are typically used in diagnostics: the hydrogen breath test (HBT) and small intestine aspirate and culture (SIAC) collected by gastroscopy [21]. Although SIAC represents the gold diagnostic standard in adult patients, this method is expensive, invasive and poorly tolerated by the patient, and requires time and appropriate preparation. In the paediatric population, caregivers may find it difficult to accept the need for general anaesthesia to collect the material in younger and non-cooperating patients. In addition, the sampling procedure itself is not standardized, and there is a possibility that the sample may be contaminated by the bacterial flora of the oral cavity. It is not uncommon to obtain false positive results caused by contamination with the microbiome of the oral cavity and oesophagus, as well as false negative results resulting from aspirate samples being taken from the proximal part of the small intestine (the middle and distal parts are endoscopically difficult to access). In addition, the method is characterised by low sensitivity and specificity [12–14, 19–22] and the repeatability of the method is estimated at only 38% [2].

The other method commonly used in the diagnosis of SIBO, and regarded by the North American Consensus on Breath Testing as the optimal one for the diagnosis of SIBO, is HBT with glucose or lactulose. It has been proposed that the SIAC method from the small intestine is unsatisfactory for the diagnosis of SIBO [9]. In contrast, breath tests offer the advantages of speed, simplicity and safety of execution, as well as low cost and non-invasiveness; in addition, general anaesthesia and invasive procedures are also generally not needed in children. The method does however have the disadvantage that the patient needs to cooperate: the child must have the ability to exhale into the prepared bag.

Unfortunately, there are no conclusive cut-off points between normal and invalid HBT values, and a major limitation of the HBT test is its low sensitivity and specificity, which vary according to the substrate used: the test demonstrates 20–93% sensitivity and 30–86% specificity when performed with glucose [23], and 31–68% sensitivity and 44–100% specificity with lactulose. Such large discrepancies may result from the significant methodological differences used in studies. In addition, there are no clear guidelines regarding the choice of whether to perform the glucose or lactulose test [22, 23]. Furthermore, false-negative results can be obtained in patients with an overgrowth of microbiome producing methane rather than hydrogen; this highlights the importance of measuring both gases by HBT [24, 25].

A study found the SIAC test from the small intestine to be positive in 62 (45%) of 139 patients with gastroenterological symptoms (flatulence, diarrhoea, feeling of fullness, weight loss, abdominal discomfort, passing more gas), while the HBT with glucose was positive in 38 (27%). The sensitivity and specificity of the HBT were 42% and 84%, respectively [21]. However, the sensitivity and specificity of the SIAC were, respectively, 40.7% and 84.0% assuming 10^3 CFU/ml as a cut-off value, and 55.3% and 83.9% assuming 10^5 CFU/ml [26]. Although breath tests such as HBT are not ideal, they are nevertheless more suitable first-line tests in patients with suspected SIBO than more invasive tests [21], especially in children with nonspecific dyspeptic symptoms [15, 16].

Although no direct assessment of the incidence of SIBO has been performed in a population of healthy children, based on positive results obtained by HBT/SIAC from the small intestine in control groups from selected studies, it has been estimated to be in the range 2.1–35% [10, 27–30] (Table 1). The incidence of SIBO has

TABLE 1. Assessment of the occurrence of small intestinal bacterial overgrowth in the paediatric population according to various authors

Author and year of publication	Characteristics of study and control groups	Diagnostic method	Group size	Frequency of occurrence of SIBO
Collins *et al.*, 2010 [10]	Children with functional abdominal pain (aged 8–18 years) and a control group of healthy children	HBT with lactulose	Study group: 75 Control group: 40	Study group: 91% Control group: 35% $p < 0.0001$
Dos Reis *et al.*, 2007 [27]	Children living in slums and a control group of children aged 5–11 with good living conditions	HBT with lactulose or glucose	Study group: 50 Control group: 50	Study group: 37.5% Control group: 2.1% $p < 0.001$
Scarpellini *et al.*, 2009 [28]	Children with irritable bowel syndrome (according to the Rome II Criteria) and a control group of healthy children (aged 5–14 years)	HBT with lactulose	Study group: 43 Control group: 56	Study group: 65% Control group: 7% $p < 0.00001$
Belei *et al.*, 2017 [29]	Overweight and obese children and a control group of healthy children (aged 10–18 years)	HBT with glucose	Study group: 125 Control group:120	Study group: 37.6% Control group: 3.3%
Belei *et al.*, 2018 [30]	Children with GERD and a control group of healthy children (aged 1–18 years)	HBT with glucose	Study group: 128 Control group:120	Study group: 31.3% Control group: 5%

GERD – gastroesophageal reflux disease, HBT – hydrogen breath test, SIBO – small intestinal bacterial overgrowth

TABLE 2. Assessment of the occurrence of small intestinal bacterial overgrowth among children taking proton pump inhibitors, according to various authors

Author	Active substance	Diagnostic method	Study group	SIBO before treatment	SIBO after treatment	p-value
Sieczkowska *et al.*, 2015 [36]	Omeprazole: 1 mg/kg, max 40 mg for 12 weeks due to inflammation of the oesophagus (confirmed histopathologically)	HBT with glucose	40 children aged 3–18 years	1 child (2.5%)	9 children (22.5%)	0.011
Cares *et al.*, 2017 [37]	Various PPI substances for > 6 months (77% children > 12 months) for GERD, eosinophilic oesophagitis, recurrent abdominal pain, dysphagia, cyclic vomiting syndrome	HBT with glucose	Study group: 56 children; control group: 27 children (healthy children, or those hospitalised for other reasons not requiring PPI; no risk of SIBO) aged 3–17 years	Not tested	Study group: 5 children (8.9%); control group: 1 child (3.7%)	0.359
Belei *et al.*, 2018 [30]	Esomeprazole 1 mg/kg, max 40 mg, for 12 weeks for GERD	HBT	64 children PPI + placebo 64 children PPI + probiotic, control group: 120 healthy children aged 1–18 years	0 0 6 (5%)	36 (56.2%) 4 (6.2%)	0.740 (PPI vs. placebo) $p < 0.001$ (PPI vs. placebo; control vs. placebo) $p = 0.090$ (control vs. PPI)
Hegar *et al.*, 2013 [38]	Omeprazole 20 mg for 4 weeks for abdominal pains	HBT with glucose	36 children PPI + probiotic 34 children PPI + placebo age > 5 years	Negative HBT as inclusion criterion	26.5% PPI + probiotic 33% PPI + placebo	0.130

GERD – gastroesophageal reflux disease, HBT – hydrogen breath test, PPI – proton pump inhibitor, SIBO – small intestinal bacterial overgrowth

been studied many times among children with various ailments: SIBO was found in 63% of children presenting with gastrointestinal symptoms (constipation, nausea and/or vomiting, diarrhoea, fetor ex ore, poor weight gain) [18], 34% of children with abdominal pain and/or diarrhoea [31], 91% of children with chronic abdominal pain [10] and 37.6% of overweight and obese children [29]. The prevalence of SIBO was also found to be 41% in children with immunodeficiency [32] and 32–37.1% in children with cystic fibrosis [33, 34].

EFFECT OF PROTON PUMP INHIBITORS ON THE GASTROINTESTINAL MICROBIOME AND SMALL INTESTINAL BACTERIAL OVERGROWTH

Although over a dozen studies on the effects of PPIs on the microbiome of the gastrointestinal tract and SIBO have been published, few of them have been conducted in children. In addition, due to significant differences in research methodology between them, it is difficult to compare their findings.

A literature review by Levy *et al.* from 2020 summarizing the effects of PPIs in children on the gut, mouth and lung microbiome found that PPIs can cause microbiome dysbiosis and their intake is associated with various pathological states, such as necrotizing enterocolitis in newborns and infants, *Clostridioides difficile* infection, SIBO, astSIAC and obesity. The authors propose that probiotic administration can restore the normal composition of the gut microbiome, but there is no clear evidence as to whether this can counteract or prevent the adverse effects caused by PPIs [35].

At the time of writing, four studies assessing the relationship between PPIs use with the risk of developing SIBO in the paediatric population are currently available (Table 2). The only available Polish publication, by Sieczkowska *et al.*, describes a prospective cohort study. The hydrogen breath test with glucose was performed before and after the treatment, and the children completed a questionnaire assessing gastroenterological symptoms. One child was found to be positive for HBT before starting treatment, and another nine (22.5%) developed SIBO after treatment with omeprazole. Interestingly, children who had normal HBT results after treatment reported significantly fewer gastroenterological symptoms (flatulence, belching, increased gas emission) than children who were diagnosed with SIBO on the basis of the HBT after treatment [36].

A previous study examined the effects of PPIs on a group of 83 children (Table 2). Small intestinal bacterial overgrowth was confirmed in five (8.9%) children from the test group and in one (3.7%) from the control group. The children who had developed SIBO had received a variety of PPI preparations: three had taken omeprazole, one lansoprazole and one esomeprazole [37].

In another study, a group of 128 children with GERD and a group of untreated controls were tested with HBT at the start and the end of a 12-week course of esomeprazole. Initially, none of the children met the criteria for the diagnosis of SIBO. The study group was divided into two: half of the children additionally received a preparation containing 0.1×10^9 CFU *Lactobacillus reuteri* DSM 17938 each day, and the other half received a placebo. After the end of the therapy, HBT was performed; SIBO was identified in 36 (56.2%) children from the placebo group and in four (6.2%) from the probiotic group. However, SIBO was also diagnosed in 6/120 (5%) children from the control group [30].

The final currently available study assessing the impact of PPIs on the development of SIBO was a randomized, double-blinded, placebo-controlled trial performed on a group of 70 children treated with 20 mg of omeprazole for four weeks. These children were divided into a study group who received a probiotic containing two strains of *Lactobacillus* (1.9×10^9 CFU *Lactobacillus rhamnosus* R0011 and 0.1×10^9 CFU *Lactobacillus acidophilus* R0052) in addition to the PPIs, and a control group who took the PPIs with placebo. All children demonstrated a normal HBT with glucose result at baseline. No significant difference in positive HBT result was observed between the two groups after four-week treatment with PPIs. The authors emphasize that taking a probiotic during PPI therapy did not reduce the risk of developing SIBO [38].

Considerably more data are available for adult patients. A meta-analysis by Su *et al*. reviewed 19 studies, 16 of which included both a group receiving PPIs and a control group that did not. In total, the analysis covered 7055 people. In three studies, SIBO was observed in the study group before and after PPIs. Among the diagnostic methods, eight studies performed SIAC, seven HBT with glucose, three HBT with lactulose, and one with D-xylose. Seven studies showed a statistically significant positive correlation between the intake of PPIs and the development of SIBO, while 12 studies did not. Interestingly, the patients taking PPIs demonstrated a significantly increased risk of SIBO, both in the studies where the diagnostic method was HBT with glucose (OR = 1.84, 95% CI: 1.03–3.30) and in those where SIAC was performed (OR = 2.22, 95% CI: 1.33–3.68). A pooled analysis of the 19 studies found the use of PPIs to be significantly associated with a moderately increased risk of SIBO (OR = 1.71, 95% CI: 1.20–2.43). The authors emphasize the significant heterogeneity in all studies included in the meta-analysis [39, 40].

A Polish study by Sieczkowska *et al.* in adults found that the incidence of SIBO was significantly higher in a group taking PPIs compared to a non-PPI group, as estimated from the abnormal HBT glucose score (44.8% vs. 21%, $p = 0.005$). The importance of using both hydrogen and methane measurements during the breath test was emphasized: in the absence of methane concentration measurements, 19.4% of patients taking PPIs and 12.9% of patients without PPIs obtained false negative results [41].

In contrast, some studies failed to confirm whether PPI treatment was associated with an increased risk of SIBO. A study by Choung *et al.* of a group of 675 adults found no significant difference in the incidence of SIBO between patients taking PPIs and those who were not. Intestinal SIAC analysis confirmed SIBO in 8% of the total group of participants; interestingly, SIBO was confirmed in 10% of the patients in the study group who were treated with PPIs (37%) [42]. Similarly, a retrospective analysis by Ratuapli *et al*. found no statistically significant relationship between the development of SIBO and PPI treatment in a group of 1191 patients following HBT examination with glucose [43].

PROBIOTIC, PROKINETICS – EFFECTIVE PREVENTION OR UNNECESSARY INTERVENTION?

Research results assessing the benefits of probiotics as an adjunctive therapy to PPI treatment are varied.

Hegar *et al*. found that combining PPI therapy with a probiotic containing *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* did not reduce the risk of developing SIBO [38]. However, Belei *et al*. reported that taking 0.1×10^9 CFU/day *Lactobacillus reuteri* DSM 17938 together with esomeprazole significantly reduced the risk of SIBO developing among children with GERD, compared to children treated with PPIs but without a probiotic [30].

As SIBO may be associated with slower gastrointestinal transit, some research has examined the efficacy of combining PPIs with prokinetic drugs; however, few studies have been performed, especially in the paediatric population. Revaiah *et al*. analysed the effectiveness of prokinetic treatment in children (> 12 years of age) and adults treated with PPIs (pantoprazole 40 mg/day, rabeprazole 20 mg/day or omeprazole 20 mg/day) for at least three months. The patients were divided into two groups: group A (91 patients) who took only PPIs, and group B (56 patients) who additionally received a prokinetic drug (levosulpiride at a dose of 75 mg/day). The hydrogen breath test with glucose was performed at the end of treatment. Small intestinal bacterial overgrowth was diagnosed in 13.18% of patients in group A and 1.78% of patients in group B. The authors conclude that adding a prokinetic drug to PPIs may reduce the risk of SIBO; however, attention should be paid to the side effects associated with long-term use of prokinetics [44].

SMALL INTESTINAL BACTERIAL OVERGROWTH TREATMENT

No diagnostic and therapeutic standards or guidelines currently exist regarding the treatment of SIBO as a result

of taking PPIs, or even SIBO itself, and therefore treatment is purely intuitive [7].

In patients who take PPIs for a gastrointestinal disease, it is not clear whether the symptoms which appear during treatment or which persist despite treatment can be attributed to the ineffectiveness of the PPIs, whether they may be side effects of treatment, or whether they may be related to the development of a new disease entity such as SIBO.

Similarly to Grzybowska-Chlebowczyk [15] and Shah *et al*. [45] in the Asia-Pacific Consensus published in 2022, the authors propose use of rifaximin as a safe and effective treatment that may be preferred due to its broad spectrum and lack of systemic side effects. Although SIBO is known to recur after treatment with rifaximin, patients re-treated with the same drug have had a good response to treatment [46]. Also Quigley *et al*. in an Expert Review suggest that therapy remains mostly empirical. Rifaximin has been the subject of a number of randomized controlled trials, but the decision on management should be individualized [47]

The only available publication found rifaximin to demonstrate good efficacy (HBT normalization in 64% of children) and safety in the treatment of SIBO in children: no side effects of the therapy were observed [48].

CONCLUSIONS

Proton pump inhibitors are safe and effective drugs that are commonly used in children in primary care, inpatient treatment and outpatient specialist care. However, they are not without side effects, such as dysbiosis of the gut microbiome, leading to the development of SIBO. Currently, it is not recommended to support the treatment of PPIs with probiotics and/or prokinetics as interventions preventing the development of SIBO. Due to the few published studies in this field, it seems that the prevalence of SIBO may be underestimated in children. This problem requires further research and the formulation of paediatric guidelines.

DISCLOSURE

The authors declare no conflict of interest.

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