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REVIEW ARTICLE

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The effects of proton pump inhibitors on the microbiome in young children

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Abstract

Aim: The use of proton pump inhibitor (PPI) treatments are increasing among paediatric patients worldwide. We aimed to review the effects of PPIs on the microbiome and its associated effect on the gastrointestinal, respiratory and metabolic systems. The role of probiotics is discussed.

Methods: We searched for relevant articles published in English language in PubMed and Google Scholar. Articles were extracted using subject heading and key words of interest to the topic.

Results: There is evidence that PPIs modify the microbiome of the mouth, gut and lungs. The specific adverse effects associated with PPIs were necrotising enterocolitis, late onset sepsis in premature infants, *Clostridium difficile* infection, asthma, obesity and small intestine bacterial overgrowth in young children. Studies on the use of probiotics to counteract adverse effects of PPIs were limited.

Conclusion: PPIs create dysbiosis of the microbiome in the mouth, gut and lungs in the paediatric population. Probiotics could restore dysbiosis but it has very poorly been studied if probiotics can counteract or prevent PPI induced adverse effects.

KEYWORDS

H2 receptor antagonist, Lactobacillus, microbiome, probiotic, proton pump inhibitor, small intestinal bacterial overgrowth

1 | INTRODUCTION

The intestinal microbiome refers collectively to the genomes of the microorganisms in the intestine and is gaining importance because the microbiome can be considered as a functional human organ with important contributions to immunity. The intestine harbours approximately 60% of the total immunoglobulins and >10^6 lymphocytes/g tissue.[1-3] In addition, the gut microbiome contributes to neural and behavioural development, as well as protective functions against pathogenic bacteria of the digestive and metabolic functions.[3]

Whether there is a close interaction between the gut microbiome and body systems is unknown. This also raises questions about the timing of the onset of the microbiome colonisation and interference. Contrary to traditional thoughts that the foetal intestine was sterile, there is indication of the presence of microbial deoxyribonucleic acid in meconium and the existence of an amniotic microbiome.[2,3] The neonatal intestine gets colonised with maternal vaginal microbes, faecal and or skin bacteria within few hours after the amniotic membrane is ruptured. A less diverse microbiome is found in babies born by caesarean section—in whom the amniotic membrane was not ruptured.[2,3] The bacteria colonising the neonatal gut can be considered as an invasion of the neonatal immune system. However, a symbiosis between the host and the new intestinal microbes is rapidly formed. While the host immune system

Abbreviations: B, Bifidobacterium; GOR(D), Gastro-oesophageal reflux disease; H2RA, Hydrogen receptor antagonists; IBD, Inflammatory bowel disease; L, Lactobacillus; LGG, *Lactobacillus rhamnosus* GG; NEC, Necrotising enterocolitis; OR, Odds ratio; PPI(s), Proton pomp inhibitor(s); RR, Risk ratio.

controls the development of the intestinal microbiome, the opposite is also true with the microbiome shaping the immune system and helping to regulate and maintain to function as an intestinal barrier.[3] Feeding is the second factor which influences the development of the microbiome in the neonate. Breast milk provides many substrates such as human milk oligosaccharides promoting bacterial growth, and it is also a natural bacterial inoculum.[1-3] Other variables influencing microbial diversity are duration of gestation, environments like neonatal intensive care unit and perinatal administration of medication.

Medication is a very common factor causing dysbiosis. Exposure starts often at birth with intrapartum administration of antibiotics and continues during infancy. For example, the most frequently dispensed prescriptions in the United States of America among infants were antibiotics, medications for the gastrointestinal system such as proton pump inhibitors (PPIs) and medication for bronchial hyper-reactivity.[4,5] These drugs are known to disturb the composition of the microbiome.[4,6] Intrapartum antibiotics prophylaxis to prevent Group B streptococcus sepsis in newborns also affects the oral and gut microbiome.[7]

The impact of PPIs and other acid-blocking medications in young infants is gaining more attention for several reasons. Firstly, there is disturbance of the microbiome. PPI usage for 8 weeks results in a decrease of *Lactobacilli* and *Stenotrophomonae* and an increase of *Haemophilus*. Additionally, the relative abundances of the phyla Firmicutes, Bacteroidetes and Proteobacteria changed significantly.[8] Secondly, there is a massive increase of off-label prescriptions.[4,5,9,10] A noteworthy fact is that before 2011 PPIs were not approved for the treatment of symptoms suggestive of gastro-oesophageal reflux (disease) (GOR(D)) in infants. When the prescribing restrictions and reimbursed claims of PPIs were lifted, its usage has increased.[4,5,9,10] The first nationwide population-based study (n = 22 643) conducted in New Zealand using individually linked patient-level administrative data to investigate use of PPI during the first year of life showed an increase from 2.4% in 2005 to 5.2% in 2012.[10] Currently, there is no alternative to treat complications of GORD such as peptic oesophagitis other than acid-blocking medications.[11]

Probiotics are known to restore the gut microbiome. However, this evidence is derived from studies on the effect of antibiotics.[12] The most common probiotic agents are *Bifidobacteria*, *Lactobacilli* and *Saccharides*.[13,14] The most recent guideline of the North American and European Paediatric Gastroenterology, Hepatology and Nutrition societies for the management of GORD do not recommend probiotics.[11] Although the study by Indrio et al[15] showed a reduction of onset of functional gastrointestinal disorders and reduction of private and public costs for their management. Yet, the use of probiotics not as a treatment for GORD, but as a balancing solution for the correction of the dysbiosis of the gut microbiome created by PPI is debatable. In this review, we have analysed the impact of PPIs on infants and children and whether probiotics could be a solution to restore dysbiosis.

Key Notes

- The usage of proton pump inhibitors (PPIs) in children is increasing worldwide.
- PPIs disturb the microbiome in the gastrointestinal and respiratory tract and are associated with necrotising enterocolitis and late onset sepsis in premature infants, *Clostridium difficile* infection, asthma and obesity in young children.
- Due to limited studies on probiotics on the microbiome effects of PPI, it is unclear whether probiotics could prevent or reverse PPI induced adverse effects.

2 | THE METABOLISM OF PPI

Proton pump inhibitors are more popular than H2-receptor antagonists (H2RAs) because they inhibit the last step of gastric acid secretion regardless of the stimulus for acid secretion.[16] PPIs need to undergo acidic activation within the parietal cell to allow ionisation and form covalent disulphide bonds with cysteines of the H–K-adenosine triphosphatase (proton pump). The proton pump is then inactivated. The volume of gastric acid that is released after stimulation, relates to the parietal cell mass and does not reach adult levels until 5-6 months after birth.[16] Despite the smaller amount of parietal cell mass, the dosages that neonates are receiving are seven-nine times higher than adult dosages.[16,17] This is in part explained by the fact that dose-related effects of PPIs in newborns have not been validated. The enzymes that clear the PPIs, cytochrome P450 2C19 and a little bit cytochrome P3A4, become at a mature level activity only at 5-6 months of life.[17] Specific single-nucleotide polymorphisms of cytochrome P2C19 [17] or infections [18] reduce clearance proportionally and increase exposure and prolong proton pump inhibition, resulting in a variation of therapeutic efficacy.[17] The metabolism of PPIs in infants is slower than in adults. Also there is a variation of the function of cytochrome P450 between populations.[19] It is important to note that bindings of PPIs such as omeprazole and rabeprazole are reversible, while others, as is the case for pantoprazole, are not.[17] The recovery of a proton pump protein has a half-life of 24 hours for omeprazole and 50 hours for pantoprazole.[16,20] Not all proton pumps are inhibited from the first dose onwards; this process needs about 3 days. PPIs are best administered 30-60 minutes before a feeding,[16,20] which is not realistic in young infants considering their feed and sleep cycle. PPIs are weak bases. Early exposure to stomach acid will greatly reduce the absorption of PPIs. Therefore, most PPIs are protected from stomach acid by a pH-sensitive enteric coating that prevents dissolution until the more neutral pH of the small intestine is encountered. This delayed release formulation slows the time of peak PPIs plasma concentration to about 1.5-3.5 hours after administration and contributes to the delayed onset of acid suppression observed with all delayed release PPIs.[21]

Proton pump inhibitors are indicated in erosive oesophagitis and non-erosive acid GORD, peptic ulcer disease and *Helicobacter pylori* infection.[11] The over-diagnosis of GORD in infants is not surprising since excessive crying, irritability and regurgitation are common reasons for parents to seek help. Many infants have been given PPIs to treat so called occult GORD hypothesising that GOR without overt regurgitation is the cause of crying and distress in infants. However, in several randomised control trials, placebo and PPI have shown similar efficacy for distress and crying.[9,11,22]

Proton pump inhibitors are associated with hypergastrinemia and hyperplasia of enterochromaffin-like cells. PPIs also induce hypochlorhydria which interferes with gastric bactericidal function, and long-term use can predispose to enteric infections, small intestinal bacterial overgrowth micronutrient deficiencies and kidney failure.[16] Studies focussing on the adverse effects of PPIs in the paediatric population specifically were to our knowledge not yet conducted.

3 | PPIS IN PRETERM INFANTS

Data from the United Kingdom show administration of a H2RA in 53% and a PPI in 23% of preterm infants.[23,24] GORD should be suspected in the presence of apnoea, bradycardia or desaturation after food intake. GORD is also associated with feeding difficulties, aspiration pneumonia and exacerbation of chronic lung disease and results often in prolonged hospital stays.[23,25] A gastric pH > 4 decreases the natural defence against gastric bacterial overgrowth. It also increases the risk for bacterial translocation, delayed gastric emptying and decreased gastric mucus viscosity.[25-27] A higher risk for necrotising enterocolitis (NEC), sepsis and mortality has been demonstrated in preterm babies treated with PPIs.[25]

A prospective randomised trial showed an increased incidence of NEC (n = 65, 21.4% vs 2.7%, P = .04) in the antacid group (H2RAs/PPI) compared with the control group [25] However, a retrospective population-based analysis did not find any increase in NEC stage 2 and above (OR 0.4, 95% CI: 0.05-3.2, P = .7) or late onset sepsis (OR 0.52, 95% CI: 0.24-1.1, P = .12), or mortality (OR 0.35, 95% CI: 0.08-1.5, P = .19).[28] Last but not least, despite the increased usage of H2RAs and PPIs in neonates, most studies have shown that there was no reduction of GOR symptoms.[16,24,25,28-32] A systematic review concluded that a meta-analysis was not possible due to lack of studies assessing the same intervention with the same outcomes.[23] Therefore, adequate powered randomised control trials in preterm infants are needed to evaluate the efficacy and safety of these commonly and probably overused antacids.

The question arises whether probiotics could re-stabilise the dysbiosis in the premature gut. Most studies looked at the effect of probiotics (*Lactobacilli*, *Bifidobacteria* or *Saccharides*) and bovine lactoferrin to prevent NEC and sepsis. The combination of both was shown to be more effective in decreasing NEC and sepsis.[13,14,33-35] Bovine lactoferrin is a normal component of colostrum and milk which enhances host defences by increasing the number of gut cells, promoting the closure of enteric gap junctions, reducing intestinal permeability and thus dissemination of gut organisms into the bloodstream.[33,36] It was not possible to determine optimal probiotic dosages, time of initiation and duration of treatment course.[14]

However, one multicentre randomised control trial which tested bovine lactoferrin supplementation with or without *Lactobacillus rhamnosus* GG vs placebo in prevention of late onset sepsis and NEC in very low birthweight preterm given acid-blocking medication, showed a reduction of late onset sepsis and a decrease of gram-negative bacilli and candida. Each day of longer exposure to PPIs would increase the risk to develop late onset sepsis with 7.7% (P = .03) in the bovine lactoferrin with or without *Lactobacillus* GG untreated group compared with 1.2% (P = .58) in the lactoferrin treated infants.[36] Similar findings were reported for NEC.[36] The risk of NEC increased 11.4% in infants who were not treated with lactoferrin, whereas this risk decreased to null for the lactoferrin group (with or without *Lactobacillus* GG. Each day of exposure to PPIs increased the risk with 4.5% of acquiring *Candida* colonisation, and administration of lactoferrin alone or with *L rhamnosus* GG significantly reduced this risk. It is an important point, since *Candida* colonisation is the most potent risk factor for *Candida* systemic infection.[36] The Cochrane review also found similar results with the administration of lactoferrin (with or without *Lactobacillus* GG) for fungemia.[33]

In conclusion, acid-blocking medication is overused in preterm infants and is a risk factor for late onset sepsis and NEC, which might possibly be reduced with additional administration of lactoferrin and some probiotic strains. However, more data are needed before recommendations can be formulated.

4 | PROBIOTICS AS POSSIBLE SOLUTION FOR INFANTS WHO ARE AT RISK FOR GASTROINTESTINAL AND LUNG PROBLEMS BY THE USE OF PPIS

Gastric acid is a major factor to prevent small intestinal or small bowel bacterial overgrowth. PPI block gastric acid and by consequence enhance the risk for small bowel bacterial overgrowth. The golden standard for diagnosing intestinal bacterial overgrowth is still an invasive test: aspiration of jejunal liquid showing over 10^5 colony-forming units of bacteria per mL.[37,38] However, in practice, two non-invasive tests are used to diagnose small intestinal bacterial overgrowth. The first one is the glucose hydrogen breath test, which is recommended by the first Rome Hydrogen-Breath Testing Consensus Conference Working Group and the second one is the methane breath test.[39] The methane breath test is not the first choice, because there is still no cut-off criteria and the test gives an additional cost.[40] The sensitivity, specificity and diagnostic accuracy of the glucose hydrogen breath test is reported to vary between 62.5%-93.0%, 78.0%-81.8% and 71.7%, respectively.[38,39,41] Two important causes of false-negative results of the glucose hydrogen breath test are due to colonisation with non-hydrogen producing bacteria or due to low detection of hydrogen levels when glucose is absorbed in the upper part of small intestine, which makes the

diagnosis of small bowel bacterial overgrowth in the lower part of the small intestine more difficult.[38,39,42]

A meta-analysis (patients >18 years, n = 7055) found that PPIs for a longer time are statistically significantly associated with intestinal bacterial overgrowth (OR 1.71, 95% CI: 1.20-2.43).[37] In children, the association of long-term use of PPIs and bacterial overgrowth has also been shown, but only in a few small studies.[38,41,43,44] A prospective cohort study (n = 40) with 3 months of PPI therapy showed that 22.6% developed intestinal overgrowth.[43] Another study reported an even higher incidence of bacterial overgrowth: 3 weeks of PPIs resulted in small bowel bacterial overgrowth in 31.2% vs 5.0% in the control group ($P < .001$, RR 1.38, 95% CI: 1.22-1.56).[41] Use of omeprazole for 4 weeks resulted in 30% with a positive glucose hydrogen breath test.[38] However, also a non-significant trend to develop bacterial overgrowth after 6 months of PPI was reported: bacterial overgrowth in 5/56 participants taking PPI vs 1/27 in the control group ($P = .359$), with a relative risk of 2.4 (95% CI: 0.29-19.6).[44]

Why is small intestinal bacterial overgrowth a problem? Small bowel bacterial overgrowth is associated with clinical symptoms such as bloating, abdominal pain, diarrhoea, nutrient malabsorption and weight loss/failure to thrive.[37,41,43,45] Children with bacterial overgrowth show a higher mean symptom frequency score for abdominal pain (2.11-0.93 vs 1.13-0.81, $P = .004$), bloating (1.33-1.1 vs 0.29-0.69, $P = .001$), eructation (1.56 −0.88 vs 0.35 −0.75, $P < .001$) and flatulence (1.33-1.23 vs 0.45-0.81, $P = .024$) than children without bacterial overgrowth.[43] This is supported by two other studies with PPI. In the study of Belei et al[41], 63.8% were symptomatic and had a glucose hydrogen breath test tested positive for bacterial overgrowth. In an Indonesian study, 13/21 (62%) developed at least one symptom compatible with overgrowth.[38] Thus, small intestinal bacterial overgrowth induces similar symptoms as those for which PPIs are often prescribed in infants. The question therefore is whether probiotics could prevent the bacterial overgrowth by restoring the imbalance. To our knowledge, only two studies have looked at this possible solution in a paediatric population. Belei et al[41], showed that children (1-18 years) with GORD treated with PPI for 12 weeks in combination with probiotics (*Lactobacillus reuteri* DSM 17938) that only 6.2% (64) ($P < .001$, RR 2.14, 95% CI: 1.61-2.84) had a positive glucose hydrogen breath test compared with 56.2% (36/64) in the placebo group. Hegar et al[38] reported a lack of efficacy of a different probiotic product: bacterial overgrowth in 33% (12/36) of the PPI-probiotic group and 26% (9/34, $P = .13$) in the PPI-placebo group. Since this was a different product *L rhamnosus* R0011 and *Lactobacillus acidophillus* R0052), these findings may confirm the specificity of each probiotic.[38]

In conclusion, PPIs are associated with small bowel bacterial overgrowth. *L reuteri* DSM 17938 might reduce bacterial overgrowth in the small intestine but more data are needed before a recommendation can be made.

The carriage of *Clostridium difficile* is as high as 37% of neonates and 30% of infants.[46,47] This is mostly due to contact with environments colonised by *C difficile* such as hospital personnel, baby baths and oximeters.[47] The reasons for the increased rates of *C difficile* infection are unknown, but changing host factors such as exposure to medication that creates intestinal microbiome imbalance is a hypothesis.[48,49] Rarely do symptoms occur before 24 months of age, because there is a lack of cellular machinery to bind and process the toxins of the *Clostridium* species.[47] In older children, antibiotics are a well-known risk factor for *C difficile* infection.[47] Antibiotic-associated diarrhoea in children occurs in 15%-20% and the most common causative agent is *C difficile* [48,49] However, according to a recent surveillance study, children with *C difficile* infection were otherwise healthy and were not exposed to antibiotics before *C difficile* infection.[50]

Proton pump inhibitors are also on the list of risk factors to develop *C difficile* infection.[47,50] Three paediatric studies have shown the association between PPIs and *C difficile* infection. The exact mechanism of PPIs induced *C difficile* infection is not well known, but a hypothesis suggests that *C difficile* spores are acid resistant. Vegetative forms which are susceptible to acidity and therefore, buffering the acidity with PPIs may allow *C difficile* to proliferate. A population-based case-control study (n = 3750) showed that acid suppression for 8-90 days was associated with *C difficile* infection in infants aged <1 year (OR 5.24, 95% CI: 1.13-24.4) and children aged 1-17 years (OR 9.33, 95% CI: 3.25-26.8).[48]When all hospitalisations, emergency room visits and antibiotic uses (n = 3321) were excluded, odds ratio was even higher (11.1 95% CI: 3.50-35.5).[48] Increased risk of *C difficile* was associated more with PPIs than H2RAs ($P < .01$) and also if there was a recent use of the drug ($P < .01$).[48] Similar results were reported in a retrospective self-controlled case series in the age group 2-18 years (n = 2531, RI 2.36, 95% CI: 2.22-2.52). Recurrent *C difficile* infection was also more likely to occur during prescription periods of PPI (RI 1.74, 95% CI: 1.51-2.00).[49] PPIs were also a high risk for *C difficile* infection (OR 8.17, 95% CI: 2.35-28.38) in non-hospitalised children (n = 1331).[50]

The American Academy of Pediatrics recommends metronidazole although the North American pulsed-field gel electrophoresis type 1 (NAP1) strain, present in 10%-19% of infected children, was resistant to this antibiotic. Vancomycin is the second choice of treatment.[47] Other possible treatment options that have been considered are probiotics. Already in 1993, the yeast *Saccharomyces boulardii* was reported to be effective in persistent *C difficile* infection in infants.[50] The yeast was reported to produce specific proteases which break down the *C difficile* toxins A and B.[51] However, the current American Academy of Pediatrics guideline and review by Esposito et al does not recommend probiotics.[47,52] A Cochrane review (13 trials) including adults and children (n = 2454) found moderate quality evidence suggesting that some probiotics are safe and effective for preventing *C difficile* infection. Among studies with a baseline risk >5%, the incidence of *C difficile* associated diarrhoea in the probiotic group was 3.1% (43/1370) compared with 11.6% (126/1084) in the control group (RR 0.30, 95% CI: 0.21-0.42, GRADE = moderate) with a number needed to treat for an additional beneficial outcome of 12.[53] Further the European Paediatric Gastroenterology, Hepatology and Nutrition society working group and the Asia-Pacific region recommend probiotics, *S boulardii* CNCM I-745.[6,12] However,

to our knowledge, no paediatric studies have been conducted to analyse if PPIs induced *C difficile* infection can be prevented and, or, treated with probiotics, although it seems logic to hypothesise that the reason for *C difficile* infection does not influence its management options.

In conclusion, PPIs are associated with *C difficile* infection in infants and children. Some specific probiotics are recommended in some guidelines. Preventing and, or, treating PPIs related *C difficile* infection in children with probiotics has not been studied yet.

Inflammatory bowel disease (IBD) was reported to be possibly associated with PPI intake. A small case-control study (mean age 15.1 ± 2.6 years) found that the odds ratios for the association of receipt of at least one prescription of PPIs or H2RAs with the risk of subsequent IBD was 3.6 (95% CI: 1.1-11.7) for PPIs and 1.6 (95% CI: 0.7-0.7) for H2RAs. However, this finding is most likely due to not recognising IBD, despite that most of the children did not have a guideline based reason to take either of the two drugs.[54] It is unclear whether probiotics in IBD are beneficial as a preventive or treatment intervention. However, it seems that some probiotics (VSL#3 and *L rhamnosus* GG) might be beneficial for acute pouchitis and to maintain remission.[54]

In conclusion, there was no association between the use of PPI and IBD.

PPI was also reported to be a risk factor to develop coeliac disease, with a stronger evidence for younger patients (OR 4.79, 95% CI: 4.17-5.51).[55] If PPIs and H2RAs were administered in combination, the risk to develop coeliac disease was higher (OR: 5.96) than if only PPIs were given (OR: 4.91), which was still a greater risk than H2RAs alone (OR: 4.16).[55] Since coeliac disease is an autoimmune disease, the hypothesis is that PPIs affect gluten digestion and absorption. However, a limitation of this study was likely confounded by protopathic bias, which means that early symptoms of coeliac disease may prompt the use PPIs prior to the final diagnosis of coeliac disease.[55] Probiotics taken by an adult population on PPI treatment for 12 weeks containing per sachet blend of probiotic bacteria containing 450 billion viable lyophilised bacteria *Streptococcus thermophilus*, *Bifidobacteriam breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei* and *Lactobacillus delbrueckii* subsp *Bulgaricus* and did not show any microbiome change and only a mild relief of symptoms.[56]

In conclusion, PPI use cannot be associated with occurrence of coeliac disease.

There is evidence coming up that PPIs also cause dysbiosis in the lungs and oropharynx. The existence of a lung-gut axis is one hypothesis, implying that due to GOR intestinal bacteria enter the respiratory tracts due to micro-aspiration and, or, that there is an alteration of the immune system due to dysbiosis that influences the healing process in the lungs.[57,58] Adult data suggested that bacterial dysbiosis in the oropharynx may lead to bacterial pneumonia.[59,60] A meta-analysis in adults showed a trend towards an association between PPIs and pneumonia, although it failed to reach significance (OR 1.42, 95% CI: 0.86-2.35, *P* = .17) (s61). PPIs were shown to change the microbiome in the oral cavity in healthy adult volunteers.[60] In a critical care unit, PPIs were associated with colonisation of gut microbes in the oropharynx.[59] To our knowledge, no studies were done in children to test the link between oropharyngeal dysbiosis due to PPIs and respiratory tract infection. But a prospective cohort study in a tertiary care centre in children aged 1-18 years old showed that PPIs promote gastric bacterial overgrowth and that non-acid reflux was associated with higher bacterial concentration in the lungs, which may show a link between PPIs use and upper and lower respiratory tract infections (s62). A multicentre study in children with GERD-related symptoms observed also a significant six-fold increase of community-acquired pneumonia in PPI users compared with the 4 months before enrolment and the control group.[45] Also a study by Orenstein et al[22] showed that lower respiratory tract infections occurred significantly more frequently in a lansoprazole group compared with a placebo group (10 vs 2, *P* = .032). However, a nested case-control study by Blank et al (n = 21 991) did not show an increase in the risk of community-acquired pneumonia or other lower respiratory tract infections resulting in hospitalisation or death in infants who were dispensed a PPI (s63). Thus, data are showing conflicting results on community-acquired pneumonia and PPI use.

A systematic meta-analysis (n = 6269) shows that probiotics decrease the incidence of respiratory tract infections in children (s64). Consumption of probiotic significantly decreased (a) the number of subjects having at least one respiratory tract infection (RR 0.89, 95% CI: 0.82-0.96, *P* = .004), (b) the number of days absent from day care/school (RR 0.94, 95% CI: −1.72 to 0.15, *P* = .02) (s64). No studies have been conducted in paediatric and adult populations to see whether probiotics prevent bacterial overgrowth in the oropharynx and lungs which are probably induced by PPI.

Cystic fibrosis patients take multi medications including PPIs. A prospective observational study showed that pseudomonas was found in 24% of the infants and was associated with crackles/wheezes and use of PPI (OR 5.47, 95% CI: 1.36-21.92, *P* = .02) or PPI and H2RA (OR 8.2:95% CI: 2.41-27.93, *P* = .001), but not H2RA alone (s65). These observations cannot prove cause and effect but add to our understanding of pulmonary manifestations of cystic fibrosis in children and that PPI might contribute to pseudomonas infection (s65).

In conclusion, concerning the lungs there seems to be a higher risk of lower respiratory infection when using PPI and dysbiosis in the oropharynx caused by PPIs may lead to bacterial pneumonia. However, further research is needed. No studies have yet evaluated the effect of probiotics in possible PPI induced lower respiratory tract infections.

5 | DO PPIS INDUCE OBESITY AND WILL PROBIOTICS DECREASE THIS EFFECT?

In the past 25 years, overweight children under the age of five has increased from 32 million in 1990 up to 42 million in 2015 (s66). It is now the most prevalent nutritional disorder globally among children (s66). An unhealthy lifestyle, increased food intake and decreasing physical activity are well-known risk factors. In addition, medication intake might also be a contributing factor for obesity. As stated earlier, the microbiome has a massive influence on the metabolic

system and many drugs influence the microbiome by creating less diversity of the intestinal gut bacteria. For a long time, a supportive association between antibiotic exposure and weight gain has been demonstrated (s67-s69). Obese children have a higher risk to develop GERD, leading to more chance of using PPIs.[11] A cohort study following infants (n = 11 089) past their initial exposure period (to PPIs) with some up to 8 year old and found that 1841 (16.6%) who used PPIs was obese with 3.85 incidence density per 100 person-years (s70). An association with increased hazard of early childhood obesity was found in relation to prolonged use of PPIs (each 30-day supply prescribed) either single or serially dispensed (hazard ratio 1.02; 95% CI: 1.01-1.03). The hazard ratio would increase with exposure to each additional medication group prescribed on top of PPIs, like antibiotics and H2RAs (s70). The impact of probiotics given in combination with PPIs on weight gain has not been tested.

In conclusion, there is an association with use of PPIs in infancy and obesity. However, until now, probiotics has not been investigated to undo this problem.

6 | PPIS RESPONSIBLE FOR SOME ALLERGIES AND PROBIOTICS CANNOT PREVENT THIS EFFECT YET

Allergic diseases are increasing in prevalence worldwide and yet the aetiology of allergic disorders is unclear (s71). The last few years there has been more evidence that PPIs increase the incidence of allergy by altering the developing microbiome (s72). One hypothesis is that due to the decreased acidity in the stomach, causing less protein breakdown, food proteins then act more frequently as allergens and induce food-specific immunoglobulin E and T helper cell-2 hypersensitivities, increasing allergic diseases (s72,s73).

The association between PPIs given early in life and allergy has been demonstrated (s72). In the group that took PPIs before the age of 6 months, the adjusted hazard ratios at a median age of 4.6 years to develop food allergy was 2.59 (95% CI: 2.25-3.00), to develop medication allergy was 1.84 (95% CI: 1.56-2.17), for anaphylaxis 1.45 (95% CI: 1.22-1.73), for allergic rhinitis 1.44 (95% CI: 1.36-1.52) and for asthma 1.41 (95% CI: 1.31-1.52) (s72). A cross-sectional study (age 7.0 ± 4.3 years) found that antacid medication was associated with an increased prevalence of food allergy (57% vs 32%) (s74). Although a case-control study found an increased association with eosinophilic oesophagitis (OR 6.05, 95% CI: 2.55-14.40) (s75). However, controversy exists because symptoms of eosinophilic oesophagitis may have been the reason to prescribe PPIs (s76). Prospective data are missing. Interestingly, in adults, an association between PPIs use and hypersensitivity reactions to drugs was found in admitted patients (RR 3.97, 95% CI: 1.97-8.29). Even after adjusting for confounders, the use of PPIs persisted as a predisposing factor (OR4.35, 95% CI: 2-9.45) (s77). However, a systematic review, showed there was no association with all the allergies, except for asthma, due to different effect measures in the included studies of the meta-analysis. It was not possible to calculate pooled estimates of the association (s74). Another meta-analysis showed that even in utero PPIs have an impact on developing asthma in the offspring (RR 1.34, 95% CI: 1.18-1.52, I2 46%, $P < .00001$) (s78).

There are no specific studies analysing the effect of combined administration of PPIs and probiotics on later allergic disease. But there is low evidence that probiotics decrease atopic dermatitis (eczema) (s71,s79-s81) and food allergy, specifically cow's milk protein allergy (s82).

In conclusion, an association with PPIs and (food) allergy has been suggested, especially for asthma. The in utero effect of PPIs given to a pregnant woman on the immune development of the newborn needs to be investigated further.

7 | PPI AS A CAUSE OFF MICRONUTRIENT DEFICIENCIES AND ROLE OF PROBIOTICS FOR PREVENTION OF THESE DEFICIENCIES

Prolonged PPI use can interfere with the absorption of some nutrients. The nutrients mainly affected with the use of PPI are iron, vitamin B12, calcium, zinc, vitamin C, magnesium, beta-carotene and fat levels. Growth retardation, poor appetite and delayed wound healing have also been reported as possible consequences of long-term PPI use (s83,s84). One paediatric study (n = 22, age 4-17 years) suggested that lansoprazole taken during 6 months was not associated with iron deficiency (s85). Gastric acidity reduces ferric iron to the more soluble ferrous form and facilitates iron absorption (s85). In adult series, the OR for developing iron deficiency was 2.49-fold higher (95% CI: 2.35-2.64) in the group taking PPIs (s83). Vitamin B12 needs gastric acidity in order to be released from foods (s83-s85). In adults infected with *H pylori* with atrophic gastritis, vitamin B12 serum level was lower in the PPIs group (s83). Vitamin C also has also been reported to be reduced in adults taking omeprazole and when there is also a *H pylori* infection the levels are even lower. However, the mechanism is unknown (s83). Similar studies have not yet been conducted in the paediatric population.

Calcium is released from the food matrix by the acidity of stomach and then absorbed in the small intestine. PPI interfere with osteoclasts because H/K ATPase pumps are also present in these cells (s83-s85). Paediatric data suggested that bone mineral content increased significantly instead of decreasing (55.9%, $P = .021$) (s85). But, a retrospective study shows that in infants PPIs use alone and together with H2RAs was associated with an increased childhood fracture hazard, resulting in an earlier median age for a first fracture (3.9 vs 4.5 years) (s86). In the elderly, an increased bone fracture risk was shown [20] (s83,s84). In adult studies, conflicting evidence has been shown (s83,s84).

Also, regarding magnesium no studies have been conducted in children. In adults, about 30 cases were reported of hypomagnesemia if PPIs were taken during more than 5 years (s83). Zinc is also an important micronutrient. In adults, plasma zinc levels decrease by using PPIs (s83,s84). Regarding beta–carotene, only one study in adults has been conducted and the inhibition of absorption that has been observed is not yet explained (s83,s84).

Fat seems to be better absorbed if the pH is higher in the stomach. The lipolytic enzyme activity increases and may improve fat absorption. Also, the conjugated and unconjugated bile becomes more soluble in an alkalic environment. For children with pancreas deficiencies, like cystic fibrosis, PPI and pancreas enzyme supplementation decrease faecal fat from 13 to 5.5 g/d (s84).

In conclusion, PPI might have influence on some micronutrient absorption but yet it is unknown whether probiotics could prevent or reverse this effect.

8 | CONCLUSION

Our literature review highlights that PPIs are associated with adverse effects such as NEC, late onset sepsis in preterm, *C difficile* infection, small intestinal or small bowel bacterial overgrowth, asthma and obesity. It is yet unknown whether the adverse effects could differ for different PPIs. Probiotics have the potential to balance the damage on the gut microbiome caused by PPI. However, more studies are needed before probiotics can be recommended in the prevention or management of most of the adverse effects due to the use of PPIs.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

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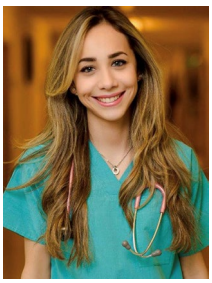
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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