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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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THE IMPACT OF PROTON PUMP INHIBITORS ON THE GUT MICROBIOME: A REVIEW

Katarzyna Jania *(Corresponding Author, Email: kasiakk19@gmail.com)*
Powiatowe Centrum Zdrowia w Otwocku Sp. z o.o., Otwock, Poland
ORCID ID: 0009-0004-4399-1016

Tomasz Antczak
Warsaw Medical University, Warsaw, Poland
ORCID ID: 0009-0006-3407-0981

Monika Gajda-Bathelt
Beskid Oncology Center – Municipal Hospital of John Paul II in Bielsko-Biała, Bielsko-Biała, Poland
ORCID ID: 0009-0006-6231-607X

Monika Dąbek
Mazovia Rehabilitation Center STOCER Włodzimierz Roefler Hospital, Pruszków, Poland
ORCID ID: 0009-0008-4403-556X

Zuzanna Perlicka
Beskid Oncology Center – Municipal Hospital of John Paul II in Bielsko-Biała, Bielsko-Biała, Poland
ORCID ID: 0009-0000-6153-7299

Karolina Smolińska
University Clinical Centre of the Medical University of Warsaw, Infant Jesus Clinical Hospital, Warsaw, Poland
ORCID ID: 0009-0001-4115-0297

Paulina Sadkowska
Independent Public Health Care Complex in Kozienice, Kozienice, Poland
ORCID ID: 0009-0000-7409-2460

Julia Kulczycka
Mazovia Rehabilitation Center STOCER Włodzimierz Roefler Hospital, Pruszków, Poland
ORCID ID: 0009-0009-9624-8273

Weronika Popow
ORLIK Medical Clinic Sp. z o.o., Warsaw, Poland
ORCID ID: 0009-0005-6680-0750

Michał Ciołkosz
Czerniakowski Hospital, Warsaw, Poland
ORCID ID: 0009-0008-7330-7069

ABSTRACT

Background: Proton pump inhibitors (PPIs) are among the most commonly prescribed medications for acid-related gastrointestinal disorders due to their high efficacy and favorable safety profile. However, emerging evidence suggests that their prolonged use may adversely affect the gut microbiome, potentially leading to clinically relevant complications.
Aim: This review aims to analyze the impact of PPI therapy on the composition and function of the intestinal microbiota.
Methods: A comprehensive literature review was conducted using databases such as PubMed and Google Scholar. Search terms included "proton pump inhibitors," "gut microbiota," "dysbiosis," and related keywords. Articles were selected based on relevance and recent contributions to understanding PPI-induced microbial changes.
Results: PPIs function by irreversibly inhibiting the H^+/K^+-ATPase enzyme in gastric parietal cells, thereby suppressing acid secretion. While beneficial in treating conditions like GERD, peptic ulcers, and Helicobacter pylori infection, PPIs also increase gastric pH, weakening the natural defense against ingested pathogens. This alteration facilitates the survival and migration of oral and exogenous microorganisms into the lower gastrointestinal tract, contributing to dysbiosis. Studies reveal significant shifts in microbial composition, including increased prevalence of Klebsiella pneumoniae, Fusobacterium nucleatum, and Campylobacter concisus. Clinically, such changes have been associated with a higher risk of small intestinal bacterial overgrowth (SIBO), Clostridioides difficile infection, and other enteric pathogens.
Conclusion: While PPIs remain a cornerstone in gastrointestinal therapy, clinicians should be aware of their potential to disrupt gut microbiota. Rational prescribing practices, guided by appropriate indications and minimal effective duration, are essential to mitigate microbiota-related risks.

KEYWORDS

Proton Pump Inhibitors (PPIS), Gut Microbiota, Dysbiosis, Side Effects of Proton Pump Inhibitors, Mechanism of Proton Pump Inhibitor, Long-Term Use of Proton Pump Inhibitors

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1. Introduction

Proton pump inhibitors (PPIs) are a group of drugs widely used in the treatment of conditions related to excessive gastric acid secretion. They are particularly effective in managing diseases of the upper gastrointestinal tract, including gastric and duodenal ulcers, ulcers caused by long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), and as part of the therapeutic regimen for *Helicobacter pylori* infection (Strand, Kim, & Peura, 2017). PPIs inhibit the production of hydrochloric acid by blocking the proton pumps in the gastric parietal cells. They are among the most frequently prescribed drugs in clinical practice, known for their efficacy and relatively favorable safety profile (Ksiądzyna, Szeląg, & Paradowski, 2015).

However, like all medications, PPIs can cause a number of side effects such as constipation, diarrhea, flatulence, nausea, vomiting, abdominal pain, headaches and dizziness, paresthesias, sleep or balance disorders, fatigue, malaise, skin reactions (e.g., pruritus, urticaria) and increased transaminase levels (Castellana et al., 2021). The severity of these symptoms and the effect of PPIs on the body depends on the duration of use, dosage and appropriateness of the indication, which is often questionable (Ksiądzyna et al., 2015).

PPIs are particularly associated with gastrointestinal disturbances, likely due to their impact on the normal intestinal microbiota. The gut microbiota comprises a complex community of organisms primarily bacteria, but also fungi, archaea, viruses, and phages that inhabit the small and large intestines, extending to the rectum (Adak & Khan, 2019). This ecosystem exists in a symbiotic relationship with the host, providing numerous physiological benefits. These microorganisms support immune defense against pathogens, synthesize vitamins such as biotin and vitamin K, produce hormones, ferment nutrients, influence brain function, and regulate intestinal activity (Wang, Zhu, Su, Gao, & Yang, 2023).

Disruption of this balanced symbiosis, known as dysbiosis, can lead to a range of complications including infections, cardiovascular, neurologic, respiratory and metabolic disorders and even cancer (Illiano, Brambilla, & Parolini, 2020). Dysbiosis may result from inadequate diet deficient in nutrients, impaired intestinal mucosa, immune system dysfunction, microbiota itself and various medications, including PPIs (Weiss & Hennet, 2017).

In this review, we have summarized the effects of PPIs use on the gut microbiome.

1.1 Aim of the study

The aim of this study is to analyze the effects of PPIs on the gut microbiome.

1.2 Method

This paper sets out to analyze the effects of proton pump inhibitors on the gut microbiome by conducting a comprehensive literature review, taking into account the latest findings in the area. The paper draws on articles from libraries including PubMed and Google Scholar. The main selection criteria included "proton pump inhibitors", "proton pump inhibitors function", "proton pump inhibitor mechanism", "side effects of proton pump inhibitors", "long-term use of proton pump inhibitors", "indications of proton pump inhibitors", "risk of proton pump inhibitors", "gut microbiota", "normal gut microbiota", "gut microbiota function", "role of gut microbiota", "mechanism of gut microbiota", "disease gut microbiota", "dysbiosis".

Relevant articles were selected, compared and contrasted with an aim of establishing effects of proton pump inhibitors on the gut microbiome.

2. Proton pump inhibitors (PPIs)

2.1 Mechanism and Function

Proton pump inhibitors are a class of drugs that include omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole. These are prodrugs, membrane-permeable weak acid-labelled bases that require an acidic environment for activation (Ahmed & Clarke, 2023). After absorption they diffuse into the parietal cells and accumulate in the acidic secretory canaliculi. The activated form of the PPIs binds covalently the potassium and hydrogen ion-dependent ATP-ase enzyme (H+/K+-ATP-ase) present in the cells lining the stomach, inactivating the pump molecule that transports protons (H+) into the gastric lumen

(Sachs, Shin, & Howden, 2006).

This irreversible inhibition of the proton pump leads to a marked reduction in gastric acid secretion and an increase in gastric pH. PPIs are active in response to stimulation of acid-secreting cells and provide long-lasting suppression of acid production.

2.2 PPIs indications

PPIs are essential in the treatment regimens of a variety of gastrointestinal conditions, including gastric and duodenal ulcers, *Helicobacter pylori* eradication, dyspepsia, gastro-esophageal reflux disease (GERD), erosive esophagitis, Barrett's esophagus (BE), suspected eosinophilic esophagitis, Zollinger-Ellison (ZE) syndrome and for the secondary prevention of gastroduodenal lesions that have arisen under treatment with nonsteroidal anti-inflammatory drugs (NSAID) and acetylsalicylic acid, and also for the prevention of recurrent hemorrhage from ulcers after successful endoscopic hemostasis (Shanika, Reynolds, Pattison, & Braund, 2023; Mössner, 2016).

PPIs are also commonly used off-label as adjunctive therapy for upper abdominal pain, nonspecific dyspepsia, prophylaxis against gastritis/duodenitis associated with corticosteroids, anticoagulants, chemotherapy and coronary heart disease (Caballero-Flores, Pickard, & Núñez, 2023; Rückert-Eheberg et al., 2022).

PPIs are approved for short-term use in children over the age of one year for the treatment of symptomatic gastroesophageal reflux disease (GERD), healing of erosive esophagitis, therapy of peptic ulcer disease, and eradication of Helicobacter pylori infection. Additionally, PPIs are considered the standard of care in the management of pediatric eosinophilic esophagitis (EoE) (Dipasquale, Cicala, Spina, & Romano, 2022).

2.3 Side Effects

Although PPIs are widely regarded as one of the safest drug classes, their use is not entirely devoid of risk. Adverse effects associated with PPIs are relatively infrequent and generally mild, encompassing gastrointestinal symptoms such as nausea, abdominal discomfort, constipation, flatulence, and diarrhea. Less prevalent manifestations include musculoskeletal issues like myopathy and arthralgia, neurological symptoms such as headache, various dermatologic reactions, micronutrient deficiencies (e.g., vitamin B12, iron, magnesium), acute interstitial nephritis, fundic gland polyps, and drug–drug interactions (notably with clopidogrel, diazepam, warfarin, phenytoin, and methotrexate) (Martín de Argila de Prados, López Cardona, & Argüelles-Arias, 2023; Kahrilas et al., 2024).

In rare cases, PPIs have been associated with hepatotoxicity, including drug-induced acute liver injury (National Institute of Diabetes and Digestive and Kidney Diseases, 2019).

3. Intestinal Microbiota: Composition and Function

3.1 Composition of the Gut Microbiota

The human microbiome consists of numerous microorganisms including bacteria, viruses, fungi, protozoa and their genetic material, which colonize the body beginning at birth (Van Hul et al., 2024). In a healthy individual, the gut microbiota is predominantly composed of bacteria from the phyla **Firmicutes** (e.g., *Lactobacillus*, *Clostridium*, *Enterococcus*) and **Bacteroidetes** (e.g., *Bacteroides*, *Prevotella*).

3.2 Function of the Gut Microbiota

The gut microbiota plays a crucial role in maintaining host physiological homeostasis and is a fundamental component of the gastrointestinal ecosystem. It contributes to the fermentation of indigestible dietary polysaccharides, leading to the formation of short-chain fatty acids (SCFAs) such as butyrate, propionate and acetate, which have both trophic and immunomodulatory functions.

Additionally, the microbiota synthesizes essential exogenous vitamins (e.g. B vitamins and vitamin K), regulates immune maturation and function through interactions with antigen-presenting cells and regulatory T cells, and provides colonizing immunity against pathogens through competition for nutrients and ecological niches.

The production of metabolites with anti-inflammatory effects and the enhancement of intestinal barrier function (tight junctions) indicate an important contribution of the microbiota to the prevention of inflammatory processes and gastrointestinal and systemic diseases (Van Hul et al., 2024).

3.3 Factors influencing microbiota

The normal bacterial flora is influenced by many factors both exogenous and endogenous. The balance and composition of gut microbiota can be significantly influenced by diet, lack of physical activity, antibiotics and others medications use, hormonal changes, environmental exposure (both overly sterile and contaminated environment), mode od baby delivery (vaginal birth vs. caesarean section), breastfeeding, underlying diseases, sleep disturbances and chronic stress (Gebrayel et al., 2022; Weersma, Zhernakova, & Fu, 2020).

Age also impacts microbial composition; for example, elderly individuals often experience a decrease in beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and an increase in potentially pathogenic genera like *Enterobacteriaceae*, *Enterococcus*, and *Clostridium* (Mangiola, Nicoletti, Gasbarrini, & Ponziani, 2018).

4. PPIs and the Microbiota

4.1 Dysbiosis

Dysbiosis refers to an imbalance in the composition and function of the microbiota within a specific ecosystem in the context in the human gastrointestinal tract. This definition is not entirely precise, as it is difficult to determine what exactly constitutes an equilibrium. Dysbiosis can also be defined as a change in the composition and functions that the microflora used to perform, or potentially the expansion of harmful microorganisms (Tiffany, & Bäumler, 2019; Iebba et al., 2016).

Causality between dysbiosis and specific diseases has not been definitively established, multiple gut-organ axes—such as the gut-brain and gut-lung pathways—support a growing body of evidence linking microbiota imbalance with allergic, metabolic, and other systemic conditions (Carías Domínguez et al., 2025)

Clinical features that may raise suspicion of dysbiosis reports symptoms such as abdominal distension, pain, and diarrhea. However, these are nonspecific and may complicate the diagnostic process (Imhann et al., 2016).

4.2 Effect of PPIs on the Microbiota

PPIs show the ability to modulate the composition and function of the intestinal microbiota, mainly by influencing the pH of gastric juice. The physiological acidity of the gastric environment plays a key role in controlling the colonization of the gastrointestinal tract by microorganisms of exogenous origin, mainly through its bactericidal effect against microflora originating from the oral cavity and the external environment.

Long-term suppression of hydrochloric acid secretion induced by PPIs results in increased survival of microorganisms in the stomach and their translocation to further sections of the gastrointestinal tract, leading to disruption of the intestinal balance.

Moreover, studies have shown a significant rise in the abundance of taxa commonly found in the oral microbiome such as *Klebsiella pneumoniae*, *Fusobacterium nucleatum* and *Camplyobacter concisus* in fecal microbiota samples from patients using PPIs. This supports the hypothesis that PPI therapy may promote intestinal dysbiosis (Imhann et al., 2016; Liang, Meng, Ding, & Jiang, 2024).

4.3 Clinical Impact of PPIs on the Microbiota

Chronic PPI use has been linked to gastrointestinal symptoms such as diarrhea, which may be associated with small intestinal bacterial overgrowth (SIBO). The dysbiosis induced by PPIs can also heighten susceptibility to enteric infections, including *Salmonella* and *Campylobacter* (Castellana et al., 2021).

Clostridioides difficile infection (CDI) has emerged as a significant concern in relation to PPIs use. Several studies have demonstrated a strong association between PPI therapy and an increased risk of CDI (Maideen, 2023) The underlying mechanism is believed to involve the elevation of gastric pH by PPIs, which may create a more favorable environment for C. difficile sporulation and growth in the intestine. Notably, the risk of *Clostridioides difficile* infection increases in a dose- and duration-dependent manner with PPI therapy (Finke et al., 2025; Freedberg, Lebwohl, & Abrams, 2014; Inghammar et al., 2021).

Moreover, studies in adults have suggested an association between proton pump inhibitor (PPI) use in children and an increased risk of enteric infections. Some evidence indicates that continuous PPI use may elevate the risk of acute gastroenteritis. CDI is the most commonly reported infection linked to PPI therapy. A large meta-analysis in children found a modest increase in CDI risk with PPI use, and retrospective data suggest that both older age and PPI exposure are associated with more severe illness (Dipasquale et al., 2022).

5. Conclusions

Proton pump inhibitors, while widely used and generally considered safe, have significant effects on the gastrointestinal microbiota. Their mechanism of reducing gastric acid secretion disrupts the natural microbial barrier of the stomach, facilitating dysbiosis characterized by the translocation and proliferation of non-native microorganisms in the gut.

This imbalance can lead to a range of clinical consequences, including increased susceptibility to infections, particularly in long-term or high-dose use. Awareness of these risks should inform the clinical decision-making process, emphasizing appropriate indication, duration, and monitoring of PPI therapy to mitigate unintended microbiota-related complications.

Authors' Contributions Statement:
Conceptualization: Katarzyna Jania, Michał Ciołkosz
Methodology: Tomasz Antczak, Karolina Smolińska
Software: Tomasz Antczak, Julia Kulczycka
Check: Weronika Popow, Karolina Smolińska
Formal analysis: Monika Gajda-Bathelt, Paulina Sadkowska
Investigation: Monika Dąbek, Katarzyna Jania
Resources: Weronika Popow, Michał Ciołkosz
Data curation: Monika Dąbek, Zuzanna Perlicka
Writing-rough preparation: Monika Gajda-Bathelt, Katarzyna Jania
Writing-review and editing: Paulina Sadkowska, Katarzyna Jania
Supervision: Zuzanna Perlicka, Julia Kulczycka

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