Effects of Helicobacter pylori Eradication Quadruple Therapy on Gastrointestinal Microbiota (Postprint)

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Abstract

Helicobacter pylori (Hp) infection and its treatment are issues of widespread global concern. However, in recent years, Hp resistance has increased and eradication rates have declined in most regions worldwide. Currently, the first-line therapy for Hp eradication is quadruple therapy, which utilizes larger antibiotic doses and longer treatment durations compared to triple therapy, thereby exerting a non-negligible impact on the gastrointestinal microbiota. This review examines the effects of Hp infection and quadruple therapy for Hp eradication on the gastrointestinal microbiota.

Full Text

Effect of Eradicating Helicobacter pylori Quadruple Therapy on Gastrointestinal Microecology

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Abstract

Helicobacter pylori (Hp) infection and its treatment are topics of global concern. However, in recent years, Hp resistance has increased and eradication rates have declined in most regions worldwide. The current first-line therapy for Hp eradication is quadruple therapy, which uses higher antibiotic doses and longer treatment courses than triple therapy, exerting a non-negligible impact

on gastrointestinal microecology. This review summarizes the effects of Hp infection and quadruple therapy eradication on gastrointestinal microecology.

Keywords: Helicobacter pylori; quadruple therapy; gastrointestinal microecology

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Helicobacter pylori (Hp) infection is the most common chronic bacterial infection globally, affecting nearly half of the world' s population. Post-infection outcomes may be asymptomatic, pathogenic, or even beneficial to the host, likely determined by the structure and composition of gastric microbiota and interactions between Hp and these microbial communities [1]. Hp is now recognized as a major causative factor in chronic active gastritis (Hp gastritis), peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. Hp also contributes to extragastrointestinal diseases such as unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. The Maastricht V Consensus Conference proposed that "Hp gastritis is an infectious disease" and stated that "unless there are competing considerations, all Hp-infected individuals should receive eradication therapy" [2].

The gastrointestinal microecosystem refers to a stable ecosystem formed by the mutual dependence and restriction between normal gastrointestinal microorganisms and the host. This system is influenced by over a hundred factors including the host' s internal environment, external environment, diet, and medications, and is closely related to disease development and progression.

1. Normal Human Gastrointestinal Microecology

The stomach harbors over a hundred bacterial species, predominantly from the phyla Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria. The most common genera are Streptococcus, Lactobacillus, and Bacteroides [3]. Gastric microbial populations are influenced by factors such as diet, proton pump inhibitors, and Hp infection [4].

Approximately 90% of human gastrointestinal microbiota resides in the intestines, which contain about 100 trillion (10^14) microorganisms with rich compositional and structural diversity. The majority are bacterial species (97.6%), with smaller proportions of archaea (2.2%), viruses (0.2%), and eukaryotes (<0.01%) [5]. The normal intestine possesses multiple barrier functions, including mechanical, microecological, chemical, and immune barriers, which effectively prevent intestinal bacteria and endotoxins from harming the host [5].

Gastrointestinal microorganisms and their metabolites influence human health by participating in host endocrine, metabolic, and inflammatory pathways. Alexandra Zhernakova et al. [6] found that archaea are closely related to chromogranin A (CgA), and elevated CgA may lead to high defecation

frequency, soft stools, and irritable bowel syndrome. Pan Fei [7] discovered that microorganisms can induce abnormal inflammatory signaling in intestinal mucosa and produce carcinogenic metabolites, promoting colorectal cancer development. Yu Ali [8] found that intestinal dysbiosis participates in the pathogenesis of chronic constipation. Hartstra et al. [9] reported that certain bacterial products, such as butyrate, can activate gluconeogenesis through gene expression and hormonal regulation, providing new clinical therapeutic insights for treating obesity and diabetes through fecal microbiota transplantation (FMT).

2. Effect of Hp on Gastrointestinal Microecology

Hp affects the distribution and quantity of original gastrointestinal flora in both animals and humans. One study using Hp strains to gavage Mongolian gerbils found that Hp infection reduced the number of original Lactobacillus in the stomach, significantly increased Bacteroides, and introduced Enterococcus and Staphylococcus aureus [10]. Hp has similar effects on human gastric microbiota. Hp infection significantly reduces microbial diversity and alters composition, with Proteobacteria, Firmicutes, and Actinobacteria being the most abundant bacterial phyla. In the absence of Hp infection, Bacteroides increase while Proteobacteria decrease [3]. Hp can also impair gastric physiological function by inhibiting gastric acid secretion. During Hp gastritis, reduced acid secretion weakens the stomach' s ability to inhibit microbial entry into the small intestine, increasing the risk of pathogenic bacterial infection.

Gastric cancer is a common malignant tumor of the digestive tract and the second leading cause of cancer-related death worldwide [11]. A foreign study on the role of gastric mucosal microbiota in intestinal-type gastric cancer development found that bacterial diversity gradually decreased from non-atrophic gastritis (NAG) to intestinal metaplasia (IM) to intestinal-type gastric cancer (GC). Additionally, the gastric microbial composition differed significantly between NAG and GC groups, with notable microbiota separation between them [12]. Wang et al. [13] demonstrated that gastric cancer patients had more diverse gastric microbiota structures, bacterial overgrowth, and enrichment of certain bacteria.

Risk factors for gastric cancer include Hp infection, atrophic gastritis (AG), intestinal metaplasia (IM), family history of cancer, inappropriate dietary habits, smoking, and alcohol consumption. Hp is a major risk factor for AG and IM and a class I carcinogen for gastric cancer. Hp virulence factors include cytotoxin-associated protein A (CagA), vacuolating toxin A (VacA), and immune factors (heat shock proteins, IL-17). Hp eradication can delay the progression of precancerous gastric lesions. Eradicating Hp before gastric mucosal atrophy occurs may prevent gastric cancer development, while in patients with existing atrophy, eradication can delay but not prevent gastric cancer onset [14].

Hp may cooperate with other bacteria to induce gastric carcinogenesis, highlighting the importance of early detection and eradication. Hp influences gas-

trointestinal microecology and disease development by altering host metabolic and inflammatory pathways through interactions with normal gastrointestinal microbiota or by affecting specific immune responses [15]. However, the protective role of Hp has gradually become recognized in recent years. Hp may induce immune tolerance and limit inflammatory responses, serving as a protective factor against intestinal immune diseases such as celiac disease (CD) [16] and inflammatory bowel disease (IBD) [17].

3. Effect of Hp Eradication on Gastrointestinal Microecology

3.1 Relationship Between Antibiotics and Gastrointestinal Microecology

The Maastricht V Consensus and Kyoto Consensus recommend quadruple therapy for Hp eradication, consisting of a PPI, bismuth agent, and two antibiotics for a 14-day course. Successful eradication primarily depends on bacterial susceptibility to antibiotics, necessitating selection of sensitive agents whenever possible. Long-term antibiotic use reduces susceptible bacteria, increases resistant strains, and may lead to multidrug-resistant organisms. Zhang et al. [18] found that metronidazole resistance can reach over 60%, clarithromycin resistance ranges from 20%-40%, and levofloxacin resistance has significantly increased, with multidrug-resistant strains rising annually. However, Hp remains relatively sensitive to tetracycline (resistance rate only 4.9%-7.3%) and amoxicillin (low resistance rate). A nationwide multicenter randomized controlled clinical study [19] reported Hp resistance rates to metronidazole, clarithromycin, and amoxicillin as 75.6%, 27.6%, and 2.7%, respectively, with 81 mixed-resistant strains among 340 Hp culture-positive isolates, consistent with Zhang' s findings [19].

Both oral and intravenous antibiotic use can affect intestinal microbial flora. Jakobsson et al. [20] studied the effects of clarithromycin and metronidazole on throat and lower digestive tract microbiota, finding that one week of antibiotic treatment rapidly decreased microbial diversity, with macrolide resistance genes still detectable four years later. This demonstrates that antibiotic use produces significant short-term and even long-term impacts on microbiota, emphasizing the need for strict antibiotic stewardship to prevent resistance development. Research indicates that antibiotic effects on gastrointestinal microbiota depend on antibiotic type, dosage, and exposure duration. For example, both oral penicillin and vancomycin can reduce Firmicutes in the intestine, though penicillin' s effect is weaker than vancomycin' s. Ciprofloxacin reduces Firmicutes and Actinobacteria (especially Bifidobacteria) while increasing Bacteroides, whereas clindamycin reduces both Bifidobacteria and Lactobacillus [21].

3.2 Relationship Between Proton Pump Inhibitors and Gastrointestinal Microecology

Proton pump inhibitors (PPIs) are acid-suppressing drugs widely used in Hp eradication and treatment of digestive diseases such as gastroesophageal reflux disease and peptic ulcers. The degree of acid suppression is a major factor affecting Hp eradication efficacy. Studies have shown that standard PPI therapy administered twice daily generally cannot sustain acid secretion inhibition, whereas increasing dosing frequency to four times daily can maintain plasma PPI levels, maximize acid suppression, increase antibiotic sensitivity, and improve Hp eradication rates [22].

A meta-analysis demonstrated a statistical association between PPI use and small intestinal bacterial overgrowth (SIBO) [23], suggesting that PPIs may cause clinical symptoms such as celiac disease, diarrhea, and bloating by altering the intestinal environment and microbiota. Overuse of PPIs also increases the risk of Clostridium difficile infection (CDI) [24]. Jackson et al. [25] used 16S rRNA technology to find that PPI users had decreased microbial diversity, significantly reduced intestinal symbiotic bacteria, and notably increased oral and upper digestive tract symbiotic bacteria, particularly Streptococcus, which increases risks of intestinal infection, pneumonia, and spontaneous bacterial peritonitis. Therefore, PPIs should be used rationally to maximize therapeutic benefits while avoiding adverse effects.

3.3 Relationship Between Mucosal Protective Agents and Gastrointestinal Microecology

Mucosal protective agents primarily refer to bismuth agents and weakly alkaline antacids. The "Management of Helicobacter pylori Infection: Maastricht V/Florence Consensus Report" recommended seven bismuth-based quadruple eradication regimens and suggested bismuth quadruple therapy in the following situations: (1) as first-line treatment in regions with high clarithromycin resistance or dual high resistance to both clarithromycin and metronidazole, with a 14-day course, and (2) as salvage therapy after failure of first-line treatments (standard triple therapy, non-bismuth quadruple therapy) and second-line treatments (fluoroquinolone-containing regimens). Dore et al. [26] found that adding bismuth could improve eradication rates for resistant strains by 30%-40%, with relatively safe short-term use but more adverse reactions than standard triple therapy, including upper gastrointestinal symptoms, dizziness, and fatigue. Similar foreign reports indicate that bismuth-containing quadruple therapy causes more adverse reactions, including upper gastrointestinal symptoms, dizziness, palpitations, metallic taste, and pain, which may result from altered intestinal microbiota composition [27].

Hp eradication helps repair damaged gastric mucosa, improve dyspeptic symptoms, promote peptic ulcer healing, and reduce the risk of malignant transformation from inflammatory changes. However, the impact of quadruple therapy on

normal gastrointestinal microecology has raised widespread concerns, including dysbiosis, small intestinal bacterial overgrowth, and Clostridium difficile colonization. Therefore, Hp eradication should prioritize sensitive antibiotics and drugs with minimal adverse gastrointestinal effects to reduce gastrointestinal side effects while achieving effective eradication.

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Note: Figure translations are in progress. See original paper for figures.