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The Effect of *Helicobacter pylori* antibiotic therapy on the microbiome

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Abstract: The emergence of the microbiome as a significant factor influencing health and disease across a number of organ systems has posed a new challenge for those wishing to identify the optimum treatments for *Helicobacter pylori* infection. This review aims to address some of these questions. There is a specific concern in the clinical setting about a spectrum of sequelae of this ranging from mild gastrointestinal upset to life-threatening conditions, such as pseudomembranous colitis, as well as overweight and obesity. The literature on the changes induced in the gut microbiota related to *H. pylori* eradication can be best considered as those which study immediate effects, short-term effects, and long-term effects. Immediate effects usually include decreased bacterial diversity, however, the use of probiotics may reduce the magnitude of change. Studies looking at short term change have consistently shown bacterial diversity to be altered three months after eradication therapy. Most of the long-term studies have shown regression to baseline microbiome diversity after one year, however, this may not be the case for quadruple therapies. Other challenges around the development of antibiotic resistance and the effect of proton pump inhibitors are also discussed.

Keywords: *H. pylori,* Microbiome, Alpha diversity, Beta diversity, Antibiotics.

Abbreviations: rRNA, Ribosomal ribonucleic acid; PPI, Proton pump inhibitor; MRSA, methicillinresistant *Staphylococcus aureus*; ESBL, extended spectrum beta lactamase.

INTRODUCTION

The emergence of the microbiome as a significant factor influencing health and disease across a number of organ systems has posed a new challenge for those wishing to identify the optimum treatments for *Helicobacter pylori* infection. Unintended consequences for the microbiome from the type of broad spectrum antibiotics such as amoxicillin, macrolides, and fluoroquionolones that are used for *H. pylori* treatment regimens are not a new concept. Antibiotic use is the single greatest risk factor for the development of *C. difficile* infection, an important cause of morbidity with significant healthcare costs, and *H. pylori* treatments have been shown to induce that condition[1,2]. More recently data have begun to emerge about the impact of eradication treatment on the microbiome in a broader sense. It is accepted that antibiotic treatment alters the diversity and composition of the gut microbiota[3-7]. Clinically, this can lead to a spectrum of disease ranging from mild gastrointestinal upset such diarrhoea, nausea, vomiting, bloating, and abdominal pain (which may lead to treatment failure by causing poor adherence to therapy) to life threatening

conditions, such as pseudomembranous colitis[2,8]. Those advocating widespread *H. pylori* eradication at the population level as a means of reducing the incidence of gastric cancer must be especially mindful of the effect of mass manipulation of the human microbiome at the population level, and the potential for harmful consequences[9,10]. For example, it has been postulated that the presence of *H. pylori* protects against overweight and obesity, with a significant association being made between exposure to antibiotics in early years of life, before the gut microbiota has become consolidated, and increased risk of weight gain[11,12]. In the stomach, an inverse association has been noted between *H. pylori* and the diversity of gastric microbiota[13]. Conversely, eradicating *H. pylori* may result in an increase in the diversity of gastric microbiota[14].

IMMEDIATE EFFECTS ON GUT MICROBIOTA

The literature on the changes induced in the gut microbiota related to *H. pylori* eradication can be best considered as those which study immediate effects, short-term effects, and long-term effects. Immediate effects refer to those noted within 2 weeks of treatment finishing. The published literature has focussed on sequencing of 16S rRNA as a means of quantifying diversity[10]. In terms of immediate effects, Jakobsson examined the effect of a standard seven-day triple therapy regime in 6 patients and noted decreased bacterial diversity[15]. A larger study of 23 patients showed that the relative abundance of Firmicutes was reduced whereas that of Proteobacteria was increased immediately after triple therapy[16]. This study had an arm who received concurrent probiotic therapy and found that probiotics reduced the magnitude of change in proportions of the gut microbiota and fewer antibiotic-resistant bacteria strains in the probiotics group. In a study of 70 patients who received bismuth-based quadruple therapy for 14 days it was noted that by day 14, α-diversity decreased and the Bacteroides to Firmicutes ratio decreased from 0.98 to 0.34[17].

SHORT-TERM EFFECTS ON GUT MICROBIOTA

The short-term effects of eradication treatment are defined for the purposes of this review as those assessed within 2-3 months after completion of therapy. Unsurprisingly, the short term effects are better studied at this point in time. There have been five studies reporting the microbiota changes within three months of treatment[15-19]. Triple therapy with proton pump inhibitor (PPI), amoxicillin, and clarithromycin for 7 days was used in three of the short-term studies[15,16,18] while bismuth-based quadruple therapy was used in two of them[17,19]. Consistently, bacterial diversity was significantly altered three months after eradication therapy. In patients treated with triple therapy, the relative abundance of Firmicutes was reduced, whereas that of Proteobacteria was increased. In patients treated with bismuth, the relative abundance of Proteobacteria was increased, whereas those of Bacteroidetes and Actinobacteria were reduced.

LONG-TERM EFFECTS ON GUT MICROBIOTA

Long-term studies are considered to be those looking at the effect on the gut microbiome six months or more after eradication therapy. Three descriptive studies assessed the long-term changes to the gut microbiota from eradication therapy, involving a total of 34 patients[15,19,20]. In all three, the α-diversity and β-diversity of the microbiota and the relative abundance of all phyla were restored to pre-treatment states at 1 year, however, there were some notable changes at the genus level.

A large-scale randomized trial from Taiwan on 1620 patients compared the long-term changes of gut microbiota observed after 14-day triple therapy, 10-day concomitant therapy, and 10-day bismuth quadruple therapy[21]. This study found that α-diversity and β-diversity were more altered in patients treated with both bismuth and non-bismuth containing quadruple therapies, compared to those treated with triple therapy. This effect was also more prolonged with α-diversity and β-diversity restored to baseline after week 8 in patients treated with triple therapy, but still not fully recovered at 1 year in patients treated with the quadruple therapies.

A useful study evaluated the impact of the two most frequently recommended first-line *H. py-*

lori eradication regimens bismuth and non-bismuth quadruple regimens — on the gut microbiota and performed 16S rRNA sequencing at 2 and 6 months after finishing treatment in 51 patients[22]. This found clinically similar eradication rates (90% in each group) and adherence. Both treatment regimens induced a significant decrease in both alpha and beta diversity two months after treatment, which was partially recovered at six months.

EFFECT ON RESISTANCE

A number of studies have illustrated that *H. pylori* eradication therapy against *H. pylori* selects out antibiotic-resistant components of gut microbiota. Standard triple therapies including a proton pump inhibitor in combination with two of amoxicillin, metronidazole or clarithromycin, were shown to promote resistant Streptococci, Staphylococci, and Enterococcus species, Enterobacteriaceae species, and Bacteroides species[23]. A separate study associated the use of triple therapy with omeprazole, clarithromycin, and metronidazole with resistance to macrolides within the gut microbiota of the host[24]. The use of fluoroquinolone-based therapies has also been associated with multi-drug resistance organisms such as MRSA (methicillin-resistant Staphylococcus aureus)[25,26] with a relative risk of 3 and extended spectrum beta lactamase (ESBL)-producing strains of *E. coli* or *K. pneumoniae*[27].

THE EFFECT OF PROTON PUMP INHIBITORS

Both resident gut bacteria and gastric acid play a significant role for a diverse range of gastrointestinal functions including the production of energy, defense against pathogens, the modulation of the immune system, and support of the integrity of the gut mucosal barrier. These can all be affected by PPI therapy[28]. PPIs are able to modify the host microbiota in each segment of the gastrointestinal tract and can contribute to dysbiosis. In addition to the gastric achlorhydria caused by PPIs, these drugs promote the survival and migration of oral bacteria to lower areas of the GI tract, which may create pro-inflammatory microenvironment[29].

CONCLUSIONS

It is clear that *H. pylori* eradication treatment has a profound impact on the microbiome of all segments of the gastrointestinal tract, and that this is not solely limited to the antibiotics used and any ensuing dysbiosis, but also the use of non-antibiotic agents, such as PPIs and bismuth. Prospective studies are necessary to elucidate how the microbial changes induced by *H. pylori* eradication therapy may impact human health, especially as the need for eradication therapy grows and success rates diminish. Long-term studies with clinical input are especially necessary in order to assess the true clinical relevance of the findings. These questions are particularly important factors for those responsible for weighing up the positive and negative effects of large scale *H. pylori* eradication schemes in order to decrease gastric cancer incidence.

Disclosures

The authors have no interests to disclose.

Specific author contributions

AOC and JPG drafted the manuscript. All authors commented on drafts of the manuscript. All authors have approved the final draft of the manuscript.

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