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Helicobacter pylori eradication in dyspepsia: New evidence for symptomatic benefit

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ABSTRACT

A causal relationship between *Helicobacter pylori* (*H. pylori*) infection and functional dyspepsia (FD) is well established in a subset of infected patients. In the Kyoto and Maastricht/Florence consensus reports H. pylori-associated dyspepsia is defined as an independent entity distinct from FD. *H. pylori* eradication is therefore the most cost-effective approach for infected patients with dyspeptic symptoms and superior to other medical therapies, such as Proton Pump Inhibitors. The therapeutic gain of H.pylori eradication for symptom relief compared to other therapeutic options is significant with the number needed to benefit of 12. Furthermore H.pylori cures chronic gastritis except in severe cases of atrophic gastritis and may prevent severe complications attributable to the infection.

Several pathophysiological mechanisms are suggested for the generation of symptoms and are related to the distinct topographic expression and degree of gastric inflammation as well as changes of gastric acid secretion, gastrointestinal motility and visceral hypersensitivity.

Introduction

Helicobacter plyori (*H.pylori*) is the most prevalent bacterial human pathogen that infects roughly 50% of the human population. Clinical observations indicate a causal relation between *H.pylori* infection and dyspeptic symptoms in a subset of patients without macroscopically visible gastric and duodenal lesions. The aim of this publication is to review current knowledge on the role of *H. pylori* infection and its treatment in patients suffering from functional dyspepsia.

Dyspepsia

Dyspepsia encompasses a spectrum of individual or combined symptoms attributable to the gastroduodenal region that include epigastric burning or pain, postprandial fullness, early satiation and nausea. A meta-analysis revealed a pooled global prevalence of 21% and identified female gender, smoking, non-steroidal drug use und *H. pylori* infection as independent risk factors [1–3]. Though life expectancy of patients with dyspepsia is not reduced [2,4], there is a substantial impact on patients' quality of life, direct medical costs, and indirect costs due to absence at the workplace and lower productivity as well as reduced household activity [5–7].

Underlying organic disease is identified in 20–30% of patients suffering from dyspepsia [8] and in lower percentages in primary care settings. Endoscopy reveals peptic ulcer disease in less than 10% and gastroesophageal cancer in less than 1% of dyspeptic patients; hence more than 70% of affected patients are classified as having functional dyspepsia [8,9].

Accordingly, current guidelines recommend empiric treatment of uninvestigated dyspepsia in the absence of alarming features or symptoms, or testing for *H. pylori* infection by non-invasive tests and treat in case of a positive test result (so call "test and treat" strategy [10–13]. Criteria for further investigation include age >45 or 60 years, depending on the guideline, with new-onset dyspepsia, gastrointestinal bleeding, dysphagia/odynophagia, persistent vomiting, unintentional weight loss, a family history of gastric/esophageal cancer, a palpable abdominal/epigastric mass and/or evidence of iron-deficiency anemia. The presence of at least one of these signs and symptoms has been associated with a 5–10% risk of serious disease, compared to only 1–2% in patients who have none [1,14].

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"Functional dyspepsia" and *Helicobacter pylori*- associated dyspepsia – different entities?

In the majority of patients with dyspeptic symptoms the diagnosis is functional dyspepsia. In 1988 the Rome consensus process group introduced the term functional dyspepsia within the group of functional gastrointestinal disorders. Applying current Rome IV criteria, functional dyspepsia is characterized by one or more of the following: bothersome postprandial fullness, early satiation or inability to finish a normal-sized meal, epigastric pain and epigastric burning that are unexplained after routine clinical evaluation including normal macroscopic findings at upper endoscopy. Two subcategories of functional dyspepsia are defined, which may overlap: postprandial distress syndrome (PDS) that is characterized by meal-induced dyspeptic symptoms and epigastric pain syndrome (EPS) that does not occur exclusively postprandially [8].

Based on evidence functional dyspepsia needs to be distinguished from *H. pylori* -associated dyspepsia. The Kyoto consensus group concluded that dyspepsia attributable to *H. pylori* involves the underlying organic infectious gastritis and thus should be categorized a specific entity apart from functional dyspepsia [15]. This separation can only be chosen if patients with *H. pylori*–associated dyspepsia remain symptom-free after 6 months following successful eradication of the infection; if symptoms persist the diagnosis is functional dyspepsia, either post-infectious or unrelated of the previous infection. Likewise, the Rome IV consensus classified *H. pylori* infection as a subgroup of secondary/organic dyspepsia (Fig. 1). However, the authors of Rome IV stated that *H pylori* infection is considered a possible cause of FD if successful eradication leads to sustained symptomatic resolution, with the efficacy of eradication on symptom control still being unclear when comparing the subgroups EPS and PDS [8]. In summary there remains controversy whether *H. pylori*-associated dyspepsia can be defined a subgroup of functional dyspepsia despite being caused by infection or represents an independent entity.

Helicobacter pylori and dyspepsia - a causal link?

The obligatory pathogen *H. pylori* is the most prevalent bacterium infecting humans. *H. pylori* infection is mostly acquired in early childhood, with the highest incidence rates in the first 5 years of life, and may persist lifelong [16]. The prevalence varies widely in the world according to the socioeconomic status of populations. An estimated 50% of the global population is infected, with declining incidence and prevalence rates worldwide since the twentieth century, particularly in populations with high hygiene standards and Western life style [16]. *H. pylori* infection is a common and curable cause of peptic gastric and duodenal ulcers, but is also linked to the development of gastric cancer and MALT lymphoma [13]. While persistent *H. pylori* colonisation virtually always leads to chronic active gastritis, it is asymptomatic in over 80% of cases [17].

The question is whether in dyspepsia *H. pylori* infection in patients is causally related or just a by chance co-incidence of

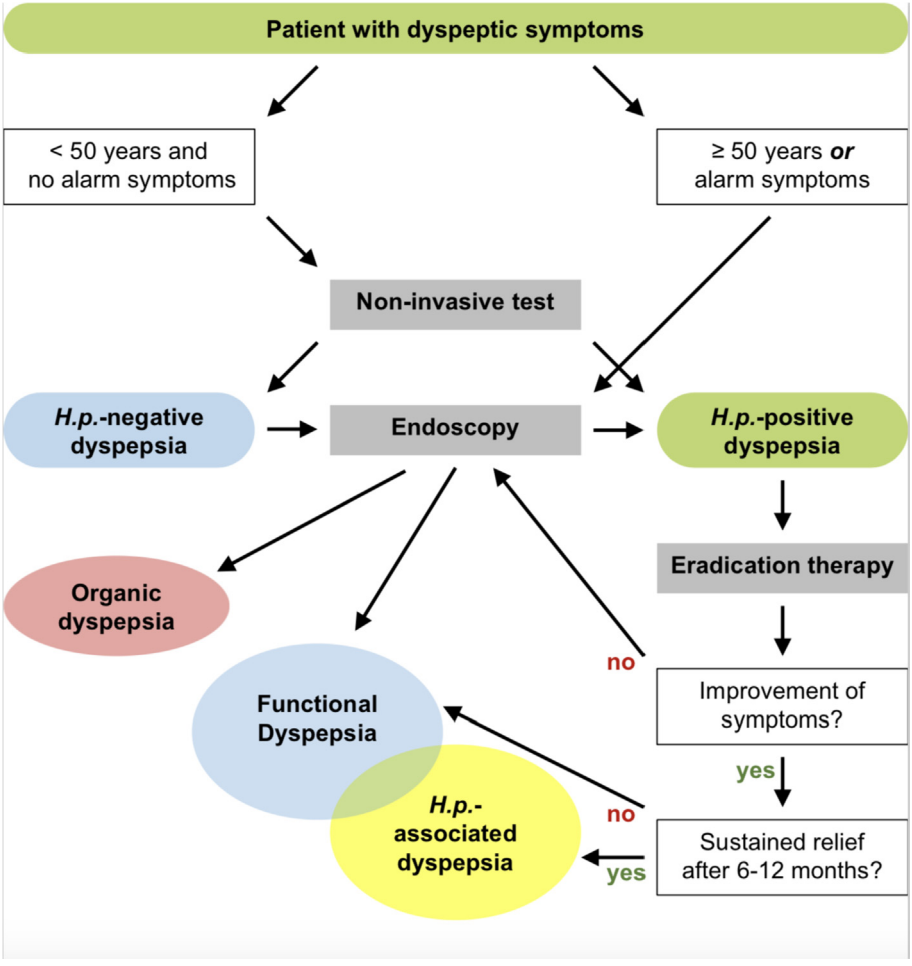

Fig. 1. Diagnostic algorithm of *Helicobacter pylori*-associated dyspepsia.

functional dyspepsia in infected persons. A causal relationship has been suggested since chronic H pylori gastritis leads to a variety of alterations in acid secretion, motility, and neuroendocrine signaling [18]. Antral predominant non-atrophic gastritis may increase acid secretion by decreased secretion of somatostatin and increased gastrin levels [13]. This effect on acid secretion could have a causal link, as some studies in FD patients showed lower duodenal ph lead to symptoms in these patients, which could possibly be mediated directly via duodenal receptors or indirectly through feedback changes in proximal gastric function [18].

In contrast persons with pan-gastritis have a higher risk mucosal atrophy and decreased acid output favoring bacterial overgrowth [13]. Gastrointestinal motility may be affected by H pylori induced increased secretion of glucagon-like-peptide-1 and decreased somatostatin release [19,20]. In spite of changes in hormonal secretion small scale human studies could not confirm disturbed gastric emptying and accommodation in relation to the infectious status [21–23], while others showed an association between *H. pylori* infection and diminished postprandial antral motility without effect on perception of gastric distension In contrast the chronic and active inflammation with release of pro-inflammatory cytokines may trigger visceral, including gastric hypersensitivity as causal factor of functional disorders including FD [35] and IBS [24,25]. Talley et al. reported an almost 12 times higher risk for suffering from FD in patients with high duodenal bulb eosinophil counts (n = 51) compared to persons without this finding (n = 48) [26]. There was no evidence of gastric eosinophilia, however duodenal eosinophilia was associated with early satiety after adjusting for age, sex and *H. pylori* status [26].

The positive association between dyspepsia and *H. pylori* infection is supported by some, although not by all studies with observational data (cross-sectional, case–control and cohort studies). *Meta*-analyis of randomized controlled intervention trials support a causal role in a subgroup of infected patients [27]. It is estimated that in about 5% of patients with functional dyspepsia the symptoms may be attributable to *H. pylori* infection [28,29]. A causal relationship is supported by the fact that acute iatrogenic or self-administered infection can induce acute dyspeptic symptoms [15,30,31], although bothering dyspeptic symptoms remain transient in the majority of those persons [31,32].

A meta-analysis of randomized controlled treatment trials with a 1 year follow up showed that *H. pylori* eradication therapy is associated with a long term resolution of dyspeptic symptoms (OR 1.38; 95% confidence interval 1.18–1.62). This effect has been consistently demonstrated in Asian, European, and American populations [33]. A Cochrane meta-analysis of 17 randomized trials involving 3566 patients reported a small but statistically significant long-term benefit of a 1 week eradication therapy on symptom relief, when compared to placebo [34]. The number needed to treat was 14 [35], whereas more recent clinical trials showed a NNT of 8 [34]. In Western populations, *H pylori* eradication therapy has resulted in a 10% therapeutic gain over placebo [35]; this rate increases to 15%–20% in studies with the same strategy conducted in Asia [36,37]. Symptom improvement rates of dyspepsia at 3 months following *H. pylori* eradication were predictive of improvement rates at 1 year [33]. Male gender and a higher body mass index were related to a better response of dyspeptic symptoms [38].

Sequential therapy was not advantageous over standard triple therapy with regard to both alleviating symptoms and eradication rates [39]. It is unresolved whether the addition of bismuth subsalicylate is beneficial for attenuating dyspeptic symptoms. The most effective *H. pylori* eradication regimen for "functional" dyspepsia to provide relief of symptoms is a metronidazole-based treatment regimen for at least 10 day, which provides an indication for a possible an association of *H. pylori*-associated functional dyspepsia and bacterial overgrowth or dysbiosis [40].

The symptomatic gain takes at least 6 months to become significant compared to no eradication, and this has been attributed to the time it takes for gastritis to resolve [15]. Given that no randomized clinical trial has allocated both *H. pylori* positive and negative patients to eradication treatment or placebo, the question whether antibiotic therapy can improve dyspepsia symptoms relief due to modification of gastrointestinal microbiota remains unanswered at this time [41].

A trial assessing the effect of eradication therapy according to individual symptoms reported in the questionnaire of patients showed a significant effect on epigastric pain and burning but not on early satiety or postprandial fullness. This suggests that patients with EPS may benefit more from eradication therapy than others [37,42]. In contrast, Fang et al. found *H. pylori* associated with only pure PDS (OR 1.86; 99.5% CI 1.01 to 3.45), but not with pure EPS (OR 1.43; 99.5% CI 0.72 to 2.84) or overlap syndrome (OR 1.12; 99.5% CI 0.55 to 2.28); the authors suggest this may be due to the higher prevalence of CagA positive strains in PDS and mediated through the severity of gastropathy in the antrum [43].

Economic analyses suggest that *H pylori* eradication may be the most cost-effective approach in dyspepsia patients if prevalence of *H pylori* infection in the population *is > 5%* [44]. The "test and treat" strategy in dyspepsia patients was reported to be more cost-effective than prompt endoscopy [45] and *H pylori* eradication was shown to be a more cost-effective approach for infected patients with dyspepsia compared with alternative medical therapies that often need to be taken long term [8]. Unwanted effects of eradication therapy include potential promotion of development of multiple-drug resistance due to widespread use of antibiotics and substantial alteration of the gut microbiota with unknown long-term consequences [27].

In countries with easy access to and low costs for upper endoscopy primary endoscopy is often considered as superior to empirical medical treatment in dyspepsia, because exclusion of organic disease by endoscopy is reassuring and therefore leads to greater patient satisfaction [7]. In addition a considerable proportion of patients who start on empirical treatment but do not improve will finally undergo endoscopy [46]. However, this is not a sufficient rationale for prompt endoscopy as the doctors' explanation is the primary measure for reassurance of patients.

Conclusion

The Rome IV criteria classify *H. pylori* associated dyspepsia as a subgroup of FD. Since this subgroup may benefit of eradication therapy test and treat strategies are recommended by current guidelines in dyspeptic patients with absence of alarming features. Due to high prevalence of FD and the fact that symptoms can be disabling it is obvious that the major social and economic burden to society implicates the important role of efficient diagnostic and therapeutic approaches.

As most patients with chronic *H. pylori* infection remain asymptomatic and studies on pathophysiological concepts explaining dyspeptic symptoms in infected patients show some controversial results. Gastric dysmotility, hypersensitivity and other possible mechanisms underly confounding factors such as diet, smoking and psychosocial stress epidemiological studies may misleading in a condition like *H. pylori* infection with major differences in prevalence in relation to geographic region and socioeconomic status. Further investigations should be conducted to understand the pathophysiological role of *H. pylori* gastritis in the absence of disease in causing symptoms.

Better comprehension of mechanisms may lead to defining more precise subgroup criteria of *H pylori* associated dyspepsia and

consequently improve diagnostic and treatment algorithms to the patients benefit.

Practice points

- *Helicobacter pylori* eradication is cost-effective in a subset of patients with dyspeptic symptoms in the absence
- H.pylori eradication therapy is superior to any other therapy for dyspepsia in patients with H.pylori gastritis.
- Several pathophysiological mechanisms are suggested to be involved in the generation of symptoms in patients with H.pylori gastritis.

Research agenda

- Better definition of patients with dyspeptic symptoms who will get a symptomatic benefit from *Helicobacter pylori* eradication
- Studies to clarify mechanisms related to symptom generation in H.pylori gastritis

Conflicts of interest

LK, LM and CS report no conflict of interest. PM has served as a speaker for Abbott Laboratories, Aptalis, AstraZeneca, Falk Pharma and Takeda.

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References

[1] Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2010;8(10):830–7. 7 e1-2.
[2] Chang JY, Locke 3rd GR, McNally MA, Halder SL, Schleck CD, Zinsmeister AR, et al. Impact of functional gastrointestinal disorders on survival in the community. Am J Gastroenterol 2010;105(4):822–32.
[3] Talley NJ, Ford AC. Functional dyspepsia. N Engl J Med 2015;373(19):1853–63.
[4] Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Effect of dyspepsia on survival: a longitudinal 10-year follow-up study. Am J Gastroenterol 2012;107(6):912–21.
[5] Brook RA, Kleinman NL, Choung RS, Melkonian AK, Smeeding JE, Talley NJ. Functional dyspepsia impacts absenteeism and direct and indirect costs. Clin Gastroenterol Hepatol 2010;8(6):498–503.
[6] Camilleri M, Dubois D, Coulie B, Jones M, Kahrilas PJ, Rentz AM, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005;3(6):543–52.
[7] Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. Aliment Pharmacol Ther 2013;38(2):170–7.
[8] Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology 2016;150(6):1380–92.
[9] Zagari RM, Eusebi LH, Rabitti S, Cristoferi L, Vestito A, Pagano N, et al. Prevalence of upper gastrointestinal endoscopic findings in the community: a systematic review of studies in unselected samples of subjects. J Gastroenterol Hepatol 2016;31(9):1527–38.
[10] Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol 2017;112(7):988–1013.
[11] North of England Dyspepsia Guideline Development G. national institute for health and clinical excellence: guidance. Dyspepsia: managing dyspepsia in adults in primary care. Newcastle upon Tyne (UK): University of Newcastle upon Tyne Crown Copyright (c); 2004. 2004.
[12] Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol 2017;112(2):212–39.
[13] Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of Helicobacter pylori infection–the Maastricht IV/florence consensus report. Gut 2012;61(5):646–64.
[14] Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006;131(2):390–401. quiz 659-60.
[15] Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015;64(9):1353–67.
[16] Blaser MJ, Chen Y, Reibman J. Does Helicobacter pylori protect against asthma and allergy? Gut 2008;57(5):561–7.
[17] Hawkey CJ, Wilson I, Naesdal J, Langstrom G, Swannell AJ, Yeomans ND. Influence of sex and Helicobacter pylori on development and healing of gastroduodenal lesions in non-steroidal anti-inflammatory drug users. Gut 2002;51(3):344–50.
[18] Koduru P, Irani M, Quigley EMM. Definition, pathogenesis, and management of that cursed dyspepsia. Clin Gastroenterol Hepatol 2018;16(4):467–79.
[19] Eda H, Fukui H, Uchiyama R, Kitayama Y, Hara K, Yang M, et al. Effect of Helicobacter pylori infection on the link between GLP-1 expression and motility of the gastrointestinal tract. PLoS One 2017;12(5):e0177232.
[20] Tham TC, Chen L, Dennison N, Johnston CF, Collins JS, Ardill JE, et al. Effect of Helicobacter pylori eradication on antral somatostatin cell density in humans. Eur J Gastroenterol Hepatol 1998;10(4):289–91.
[21] Leontiadis GI, Minopoulos GI, Maltezos E, Kotsiou S, Manolas KI, Simopoulos K, et al. Effects of Helicobacter pylori infection on gastric emptying rate in patients with non-ulcer dyspepsia. World J Gastroenterol 2004;10(12):1750–4.
[22] Thumshirn M, Camilleri M, Saslow SB, Williams DE, Burton DD, Hanson RB. Gastric accommodation in non-ulcer dyspepsia and the roles of Helicobacter pylori infection and vagal function. Gut 1999;44(1):55–64.
[23] Chang CS, Chen GH, Kao CH, Wang SJ, Peng SN, Huang CK. The effect of Helicobacter pylori infection on gastric emptying of digestible and indigestible solids in patients with nonulcer dyspepsia. Am J Gastroenterol 1996;91(3):474–9.
[24] Gerards C, Leodolter A, Glasbrenner B, Malfertheiner PH. Pylori infection and visceral hypersensitivity in patients with irritable bowel syndrome. Dig Dis 2001;19(2):170–3.
[25] Hughes PA, Harrington AM, Castro J, Liebregts T, Adam B, Grasby DJ, et al. Sensory neuro-immune interactions differ between irritable bowel syndrome subtypes. Gut 2013;62(10):1456–65.
[26] Talley NJ, Walker MM, Aro P, Ronkainen J, Storskrubb T, Hindley LA, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007;5(10):1175–83.
[27] O'Connor A, O'Morain CA, Ford AC. Population screening and treatment of Helicobacter pylori infection. Nat Rev Gastroenterol Hepatol 2017;14(4):230–40.
[28] Moayyedi P, Forman D, Braunholtz D, Feltbower R, Crocombe W, Liptrott M, et al. The proportion of upper gastrointestinal symptoms in the community associated with Helicobacter pylori, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Leeds HELP Study Group. Am J Gastroenterol 2000;95(6):1448–55.
[29] Malfertheiner P, J MO, Fischbach W, Layer P, Leodolter A, Stolte M, et al. Helicobacter pylori eradication is beneficial in the treatment of functional dyspepsia. Aliment Pharmacol Ther 2003;18(6):615–25.
[30] Morris A, Nicholson G. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH. Am J Gastroenterol 1987;82(3):192–9.
[31] Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfil Koch's postulates for pyloric Campylobacter. Med J Aust 1985;142(8):436–9.
[32] Graham DY, Opekun AR, Osato MS, El-Zimaity HM, Lee CK, Yamaoka Y, et al. Challenge model for Helicobacter pylori infection in human volunteers. Gut 2004;53(9):1235–43.
[33] Zhao B, Zhao J, Cheng WF, Shi WJ, Liu W, Pan XL, et al. Efficacy of Helicobacter pylori eradication therapy on functional dyspepsia: a meta-analysis of randomized controlled studies with 12-month follow-up. J Clin Gastroenterol 2014;48(3):241–7.
[34] Mazzoleni LE, Sander GB, Francesconi CF, Mazzoleni F, Uchoa DM, De Bona LR, et al. Helicobacter pylori eradication in functional dyspepsia: HEROES trial. Arch Intern Med 2011;171(21):1929–36.
[35] Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;(2):Cd002096.
[36] Gwee KA, Teng L, Wong RK, Ho KY, Sutedja DS, Yeoh KG. The response of Asian patients with functional dyspepsia to eradication of Helicobacter pylori infection. Eur J Gastroenterol Hepatol 2009;21(4):417–24.
[37] Lan L, Yu J, Chen YL, Zhong YL, Zhang H, Jia CH, et al. Symptom-based tendencies of Helicobacter pylori eradication in patients with functional dyspepsia. World J Gastroenterol 2011;17(27):3242–7.
[38] Kim SE, Park YS, Kim N, Kim MS, Jo HJ, Shin CM, et al. Effect of Helicobacter pylori eradication on functional dyspepsia. J Neuro Gastroenterol Motil 2013;19(2):233–43.
[39] Sarikaya M, Dogan Z, Ergul B, Filik L. Functional dyspepsia symptom resolution after Helicobacter pylori eradication with two different regimens.

Przegląd Gastroenterol 2014;9(1):49–52.
[40] Kim YJ, Chung WC, Kim BW, Kim SS, Kim JI, Kim NJ, et al. Is Helicobacter pylori associated functional dyspepsia correlated with dysbiosis? J Neuro Gastroenterol Motil 2017;23(4):504–16.
[41] Holtmann G, Talley NJ. Functional dyspepsia. Curr Opin Gastroenterol 2015;31(6):492–8.
[42] Talley NJ, Walker MM, Holtmann G. Functional dyspepsia. Curr Opin Gastroenterol 2016;32(6):467–73.
[43] Fang YJ, Liou JM, Chen CC, Lee JY, Hsu YC, Chen MJ, et al. Distinct aetiopathogenesis in subgroups of functional dyspepsia according to the Rome III criteria. Gut 2015;64(10):1517–28.
[44] Fischbach W, Malfertheiner P, Lynen Jansen P, Bolten W, Bornschein J, Buderus S, et al. [S2k-guideline Helicobacter pylori and gastroduodenal ulcer disease. Z Gastroenterol 2016;54(4):327–63.
[45] Mahadeva S, Chia YC, Vinothini A, Mohazmi M, Goh KL. Cost-effectiveness of and satisfaction with a Helicobacter pylori "test and treat" strategy compared with prompt endoscopy in young Asians with dyspepsia. Gut 2008;57(9):1214–20.
[46] Madisch A, Miehlke S, Labenz J. Management of functional dyspepsia: unsolved problems and new perspectives. World J Gastroenterol 2005;11(42):6577–81.