Helicobacter pylori: Historical therapy and current treatment

Helicobacter pylori – dotychczasowa terapia i leczenie współczesne

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This is a translated article.

Please cite the original

Polish-language version as


DOI

10.17219/pzp/118082

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Abstract

Helicobacter pylori (H. pylori) infection is a cause of gastritis, which in consequence may lead to gastric ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma or a cancerous process. It is estimated that this bacteria, being an oncogenic factor, exists in the gastrointestinal tract in more than half of the world population. This proportion varies according to the level of economic development of a given country; in highly developed countries it can be only 24%, while in developing countries it reaches even 70%. The maximal efficacy of H. pylori eradication is up to 90% and the issue of antibiotic resistance is a major clinical problem. There are 56.7% strains with metronidazole resistance and 55.2% strains with clarithromycin resistance in Lower Silesia. The latest guidelines of the Maastricht V/Florence 2016 Consensus confirm that probiotics containing Saccharomyces boulardii, Lactobacillus or Bifidobacterium may increase the percentage of eradication. Moreover, the intake of broccoli sprouts in the diet may support the treatment of H. pylori infection. The aim of this study is to present and compare the historical methods of therapy to the current treatment. This paper presents invasive and non-invasive methods of diagnosis. Moreover, the way of discovering H. pylori, the characteristics of this bacteria with its pathogenicity and basic epidemiological information are covered.

Key words: Helicobacter pylori infection, probiotics, Helicobacter pylori eradication, antibiotic resistance
The history of *Helicobacter pylori* (*H. pylori*) is inseparable from the history of *Homo sapiens*. This is proven by genetic analyses, according to which the bacterium probably originates from East Africa and spread around the world about 58,000 years ago with the expansion of modern human. Studies show a correlation between strain diversity and human genetic diversity and geographical distribution.¹

The first mention of spiral bacteria existing in the stomach dates back to 1875. Georg Bottcher and Michel Letulle observed these microorganisms back then, but were unable to culture them and probably because of that they did not conquer the scientific world with this discovery.² The author of subsequent descriptions from 1893 is Giulio Bizzozero, who discovered bacteria that exist in the acidic environment of a dog’s stomach.³ Another milestone was in 1889, when Polish professor Walery Jaworski first described in detail the presence of “cochlear”, “spiral” bacterium in human gastric fluids. He called it *Vibrio rugula* and concluded that it could be an etiological agent of gastritis.⁴

Jaworski’s discovery did not have a significant impact on the scientific world at that time for 2 reasons: firstly, it was published only in Polish in *Podręcznik chorób żołądka i dyetetyki szczegółowej*, and secondly, it met with considerable criticism from the scientific community. Franz Boas (authority in the area of gastrointestinal diseases and discoverer of Boas–Oppler bacillus) showed that he was able to obtain morphologically similar shapes as by-products of a chemical reaction between the gastric mucosa and hydrochloric acid.⁵

However, the real breakthrough came only in 1982, over 90 years after Jaworski’s discovery, when *H. pylori* in vitro culture started.⁶ It was a success of 2 Australians – Barry James Marshall and Robin Warren. In 2018, Marshall drank the bacterial suspension himself after a control endoscopy to prove the role of bacteria in the pathogenesis of gastric ulcers and gastritis. Just a few days later he complained about nausea and unpleasant smell from his mouth, and then vomiting appeared. Endoscopy results on the 8th day of the experiment were obvious – advanced gastritis, and from the biopsy *H. pylori* was cultured, which thus became a confirmed etiological factor of gastritis.⁷ In 2005, Marshall and Warren were awarded the Nobel Prize in Physiology and Medicine.⁸

**Characteristics of *H. pylori***

*Helicobacter pylori* is a Gram-negative, catalase- and oxidase-positive, helical-shaped bacillus bacterium. It has 4–6 flagella at the pole, which allow it to move. It is a facultative anaerobe and needs carbon dioxide (CO₂) to grow. There is a layer of glycocalyx on its surface, which determines its hydrophobicity and negative charge. In the acidic environment of the stomach, this layer is partially removed, exposing hydrophobic spots that allow adhesion to the cells of stomach epithelium.⁹ The outer membrane of the microorganism contains a lipopolysaccharide (LPS) composed of lipid A, an oligosaccharide core and side-chain O. Compared to other bacteria, lipid A shows little biological activity and side-chain O can “mimic” Lewis blood groups, making it easier for the bacteria to avoid reactions from the host immune system. The LPS has the capacity for genetic variability, which makes it possible to adapt to the conditions of the gastric mucosa and also ensures population diversity. The genome encodes a number of outer membrane proteins, such as porines, adhesines, iron transporters, or a set of proteins with previously unknown functions.

*Helicobacter pylori* also has the ability to respond quickly to changes in the environment, which results in changes in the transcription of specific genes responsible for coping with stress. The response of bacteria to environmental stress is multi-factorial and can be initiated by using multiple interconnected regulatory systems.⁸

An important role in pathogenesis is played by the *vacA* genes encoding the vacuolating toxin secreted by the bac-
terium, which is responsible for the destruction of epithelial cells. In culture, it causes the formation of vacuoles in stomach cells and leads to their destruction. The \( \text{vacA} \) gene consists of 2 variable parts – the \( s \) region present in the form of \( s1a \) and \( s2 \) alleles, and the \( m \) region in the form of \( m1 \) and \( m2 \) alleles. The combination of alleles of the \( s \) and \( m \) regions determines the production of cytotoxin by a given strain. The \( s1a \) variant of the \( \text{vacA} \) gene shows a higher pathogenicity than \( s1b \), while the \( s2 \) variant is more commonly found in connection with the diagnosis of gastric ulcer disease. Moreover, the \( m1 \) variant causes much greater damage to the gastric mucosa than the \( m2 \) variant. Additionally, the \( \text{cagA} \) gene (cytotoxin-associated gene) is used as a marker to detect the presence of \( \text{cag} \) pathogenicity islands. Several \( \text{cag} \) island genes are responsible for encoding proteins increasing the virulence of a strain. The microorganism produces urease, which is important in the diagnosis of infections and also provides protection against gastric acid.

**Epidemiology of \( H. \text{pylori} \)**

*Helio**bacter pylori* is a widespread pathogen that has been living in human bodies for many thousands of years. It is the first formally recognized bacterial carcinogen and the main etiological agent of gastric ulcers and other gastrointestinal diseases. The infection affects all parts of the world and studies show the presence of this bacterium in more than half of the living population, although there are differences in infection frequency among countries.

Man is the main reservoir of this microorganism and the infection is spread through secretions (saliva, vomit) and excretions through oral–oral and fecal–oral routes. Young children are particularly exposed to the infection, most often the patients under the age of 12.

Bacteria excreted with feces may be present in the aquatic environment in the form of endospores, so it is assumed that water is an important route for the pathogen to spread. This mainly concerns countries with a low socio-economic status. The regions with the highest infection rate include Africa (approx. 70%), South America (69%) and Western Asia (65%), while in highly developed countries, the infection rate is much lower and reaches 37% in North America, 34% in Western Europe and 24% in Oceania. Poland is one of the countries with a high infection rate. According to the research, the percentage of people infected in our country reaches approx. 84% in adults and approx. 32% in people up to 18 years of age.

Childhood is a particularly important period in the process of *H. pylori* infection. It has been shown that the invasion takes place at an early age, and that poor socio-economic conditions are most conducive to it. Contact with infected individuals appears to be the main route for the spread of the pathogen. As urbanization increases, the number of *H. pylori* infections decreases in the West. According to the studies conducted in the USA, Europe and Japan, the number of infection cases decreases by 25% per decade.

**Diseases induced by \( H. \text{pylori} \)**

**Chronic gastritis**

Chronic gastritis is a condition in which a chronic inflammatory infiltration is present in the gastric mucosa, leading to metaplasia and its gradual disappearance.

Colonization of the gastric and duodenal mucosa with *H. pylori* bacteria is considered to be the main cause of their chronic inflammation. The bacteria can be found in the mucus covering the membrane. The characteristic histological picture in the course of this disease is intestinal metaplasia, atrophy and neutrophil infiltration. Inflammation develops as the sum of the influence of toxins and enzymes secreted by bacteria and chemical compounds released by the activated neutrophils. The course of the disease is usually subclinical and sometimes even asymptomatic. Usually, the symptoms of dyspepsia are found: nausea, vomiting and a feeling of discomfort in the abdomen. Sometimes, when there is an extensive loss of gastric mucosa cells, hypochlorhydria or achlorhydria can be diagnosed.

The final clinical outcome depends on the extent and location of the infection. When an effective treatment is applied, the health condition improves significantly, but the cessation of inflammatory infiltration may take much longer. Chronic gastritis has a considerable bearing on the occurrence of peptic ulcers and the development of stomach cancer.

Infection with *H. pylori* always leads to active chronic gastritis, which then causes gastric or duodenal ulcers in 1–10% of cases.

**Peptic ulcer disease**

A peptic ulcer is defined as a cavity in the mucous membrane that reaches beyond its muscularis mucosae. The presence of inflammatory infiltration in its surroundings is characteristic. Peptic ulcer disease is one of the most common gastrointestinal diseases. The incidence rate among men is twice as high as among women.

Infection with *H. pylori* together with the abuse of non-steroidal anti-inflammatory drugs are the main causes of the peptic ulcer development. In most cases, it is located in the duodenum.

The bacterium has the ability to produce urease, which decomposes urea. As a result of this reaction, ammonium ions are formed in the stomach to neutralize hydrochloric acid. The pH in the stomach is lowered, which activates the pathological secretion of gastrin, a hormone that increases the secretion of hydrochloric acid by the stomach. The gas-
tric mucosa is irritated, and a peptic ulcer develops at the sites of contact with hydrochloric acid. The penetration of strongly acidified gastric contents into the duodenum induces the development of the ulcer in this place.

Whether the infection with *H. pylori* will cause the development of the disease is also determined by the genetic characteristics of the bacteria. In the vast majority of patients with peptic ulcer symptoms, an infection with the *cagA* gene strain was found. It constitutes one of many genes determining the pathogenicity of bacteria.

Genetic predispositions are also important factors in the development of gastric ulcer disease, as well as other agents, such as smoking, alcohol consumption and diet, which may increase the risk of the disease.

*Helicobacter pylori* is responsible for the formation of more than 75% of duodenal ulcers and 70% of stomach ulcers; therefore, the eradication of bacteria is a very important step during treatment. Moreover, pathogen removal reduces the risk of recurrence of ulcers and bleeding from the ulcer by 10–15 times. In patients who have not undergone antimicrobial treatment, the recurrence of bleeding during the year occurs in 25% of cases, and after successful eradication, the risk decreases completely.\(^{17}\)

### Stomach cancer

Chronic atrophic gastritis in *H. pylori* infection may cause gastric cancer.\(^{18}\) The eradication of bacteria in asymptomatic infected persons, and in persons after endoscopic gastric cancer resection, reduces the risk of gastric cancer.\(^{19}\)

### MALT lymphoma

Mucosa-associated lymphoid tissue (MALT) lymphoma is a lymphatic tissue cancer of the digestive tract. It is usually located in the stomach. Long-term gastric mucositis caused by *H. pylori* is found in 90% cases of this tumor.\(^{20}\) Scientific studies have shown that *H. pylori* is involved in the initiation and progression of MALT lymphoma.\(^{21}\) The eradication of bacteria has been shown to cause complete histological regression of low-grade malignant lymphoma.\(^{22}\)

### The effect of *H. pylori* on diseases outside the gastrointestinal tract

*Helicobacter pylori* has been shown to be associated with unexplained iron-deficiency anemia, idiopathic thrombocytopenic erythema and vitamin B\(_12\) deficiency. The eradication of *H. pylori* in chronic hives and rosacea also brings beneficial effects.

The effects of bacteria on asthma, chronic obstructive pulmonary disease, coronary arterial disease, ischemic stroke, Raynaud syndrome, Parkinson’s and Alzheimer’s diseases, Sjögren’s syndrome, metabolic syndrome, diabetes mellitus type 2, and fibromyalgia, are still under study, and the results to date are not conclusive.\(^{23}\)

### Diagnosis of *H. pylori* infection

The diagnostic methods can be divided into invasive and non-invasive. Invasive methods require gastroscopy with biopsy. It is recommended to perform them in the presence of dyspeptic signs and symptoms (pyrosis, bloating, belching). The section should be taken from the pars prepylorica region, where bacteria may be present. Cardia, fundus and corpus are the regions where bacteria may be present in patients taking proton-pump inhibitors (PPIs).\(^{24}\) The material collected may be tested for urease production, or be subject to histopathological evaluation for early detection of possible neoplastic changes or culture establishment. Unexplained iron-deficiency anemia, idiopathic thrombocytopenic erythema and vitamin B\(_12\) deficiency are the reasons to search for an infection.

Non-invasive methods include: urease production test (respiratory test, urine test), stool test detecting antigens that are produced by live *H. pylori* bacteria, serological test, and polymerase chain reaction testing (PCR) (stool or saliva sample). The gold standard of diagnosis is the urease breathing test (UBT), which does not require gastroscopy. The patient is administered orally a dose of \(^{13}\)C-labelled urea, or less commonly \(^{14}\)C radioisotope, which is broken down in the stomach by bacterial urease into ammonia and CO\(_2\). The amount of labelled CO\(_2\) in the exhaled air correlates with the presence of *H. pylori* in the stomach. The measurement is made after 15–30 min; the test is characterized by high sensitivity (90–95%) and specificity (90–98%). The selection of the method depends on the current clinical situation of the patient and the need to perform endoscopy of the upper gastrointestinal tract.\(^{24}\)

Test-and-treat strategy consists in conducting a non-invasive test and performing eradication in case of a positive result. In Poland, it is used exclusively in younger patients (under 45 years of age) due to a higher risk of developing stomach cancer without alarming symptoms, such as weight loss, dysphagia, overt gastrointestinal bleeding, tumor in the abdominal cavity, or iron-deficiency anemia. In the elderly, or when alarming symptoms occur, an endoscopic examination of the upper gastrointestinal tract is necessary.\(^{25}\)

According to the Kyoto Global Consensus, *H. pylori* infection has been identified as an infectious disease that requires treatment regardless of whether the infection is clinically symptomatic or asymptomatic.\(^{26}\)

### Treatment methods used to date

The first treatment method of *H. pylori* infection was created in 1987 by Thomas Borody, an Australian gastro-
enterologist born in Cracow. He worked then with Marshall and Warren. It was a triple therapy consisting of bismuth, metronidazole and tetracycline. It soon became common in the USA.

Over the years, the number of new reports on the infection and treatment regimens has been increasing. Therefore, in 1997, the European *Helicobacter pylori* Study Group organized a meeting in Maastricht for *H. pylori* specialists, primary care physicians and representatives from national gastroenterological societies. The Maastricht consensus meeting was attended by 63 participants from 19 European countries, as well as observers from Canada, Japan and the USA. During the meeting, it was concluded that the treatment should be simple, well-tolerated, easy to implement, and cost-effective. Additionally, some modifications concerning the drugs used in eradication therapy were established. A classic triple therapy based on bismuth was replaced by triple therapy consisting of PPIs and 2 antibiotics (optionally: clarithromycin, metronidazole and amoxicillin). The literature and clinical experience of that time indicated a higher efficiency, a lower number of adverse effects and patients’ better amenability to this treatment regimen.27

Another meeting was held in Maastricht in 2000. Then the therapy was modified. New guidelines recommended using PPIs or bismuth along with clarithromycin and amoxicillin or metronidazole in the therapy of the first choice. Numerous studies proved the same efficiency of bismuth regimens and PPIs regimens. The therapy of the second choice should be quadruple and consists of PPIs, bismuth, metronidazole, and tetracycline. If bismuth is not available, the therapy of the second choice can be triple therapy based on PPIs.28

Maastricht III Consensus Report of 2005 indicates that the guidelines concerning the first choice of the first have remained unchanged: it is still PPIs, clarithromycin and amoxicillin or metronidazole if the immunity to clarithromycin in a given area is less than 15–20%. In addition, there were indicated the advantages of using metronidazole instead of amoxicillin in the areas where the immunity is lower than 40%. Also, 14-day treatment was found superior to 7-day treatment. The quadruple bismuth therapy was recognized as an alternative treatment to the therapy of the first choice and remained the main therapy of the second choice. If not available, PPIs, amoxicillin or tetracycline were recommended as the therapy of the second choice.29

The triple PPIs, clarithromycin and amoxicillin or metronidazole treatment has become widespread because it was recommended by all conferences held up-to-date. However, as years passed, its efficiency lowered and allowed up to 70% of patients to be cured. This resulted mainly from increasing antibiotic resistance in bacteria against clarithromycin. In 2012, during the Maastricht IV/Florence Consensus meeting, despite not developing any new cure, the studies on using different combinations of drugs used so far were analyzed. The sequential treatment, which consists in 5-day PPIs with amoxicillin therapy, and then 5-day PPIs, clarithromycin and metronidazole therapy, has gained recognition. It was also proposed to take 3 antibiotics simultaneously with PPIs (the quadruple therapy without bismuth). An old formula consisting in the quadruple therapy with bismuth has been renewed due to developing galenical formula containing bismuth salts, tetracycline and metronidazole in 1 pill.30

**Contemporary treatment**

Nowadays, in accordance with the guidelines of the Maastricht V/Florence 2016 Consensus Report,25 the following treatment regimen for *H. pylori* infection is applied:

- **triple therapy** – consists in the application of PPIs and 2 out of 3 antibiotics listed below: amoxicillin, clarithromycin and 5-nitroimidazole derivative (metronidazole or tinidazole);
- **bismuth quadruple therapy** – based on a bismuth compound, PPIs and 2 antibiotics (usually tometronidazole in combination with tetracycline). It is also possible to administer levofloxacin, amoxicillin, rifabutin, or furazolidone;
- **non-bismuth quadruple therapy** – has 3 possible variants. The 1st one is simultaneous therapy, which consists in the application of PPIs, amoxicillin, clarithromycin, and nitroimidazole derivative for 10–14 days. The 2nd variant – sequential therapy – consists in the application of PPIs and amoxicillin for 5–7 days, and then clarithromycin and nitroimidazole derivative. The 3rd variant of non-bismuth quadruple therapy is a hybrid therapy – during the first 7 days only PPIs and amoxicillin are administered, then clarithromycin and nitroimidazole derivative;
- **fluoroquinolone therapy** – can be quadruple or triple. The former consists of PPIs, amoxicillin, fluoroquinolone (mainly levofloxacin, sometimes moxifloxacin), and bismuth compound. Triple fluoroquinolone therapy consists of the same elements as the quadruple one, but without bismuth compound.25

**Resistance**

The main reason for the failure of *H. pylori* eradication is the development of resistance by the bacteria. Currently, there is a high level of resistance of bacteria in Poland. The research conducted in Lower Silesia in 2011–2013 showed the existence of 56.7% of strains resistant to metronidazole, 55.2% – to clarithromycin and 5.9% – to levofloxacin. Double resistance was detected in 32.8% of cases. Resistance to amoxicillin has not been detected yet.31
If treatment regimen fails, an antibiotic susceptibility test should be performed and the therapy should be adjusted to antibiogram.

**Probiotics**

Probiotics, as defined by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), are living microorganisms which, when administered in a sufficient amount, have a beneficial effect on the health of the host.32 Can they help in *H. pylori* eradication? It turns out that probiotics have both direct and indirect inhibitory effects against *H. pylori*, indicated both in animal models and in clinical trials.33 Their application as adjuvant therapy for the traditional treatment of *H. pylori* increases the eradication level while reducing adverse effects.34 So why is there controversy over their routine use? Dozens of various probiotic preparations are available in Poland, but not all of them have been tested for efficacy, and only a few are registered as medicinal products.35 They are often multi-component, heterogeneous preparations differing in bacterial strains and their doses, so they are difficult to compare.

Official guidelines of the 2016 Maastricht V/Florence Consensus indicate that preparations with strains of *Saccharomyces boulardii* (S. boulardii), *Lactobacillus* or *Bifidobacterium* can increase *H. pylori* eradication rates by improving therapy tolerance, mainly by reducing diarrhea incidence.25

Among the probiotic preparations, a preparation with *S. boulardii* strain, whose efficiency is well documented, deserves special attention.36 A meta-analysis of 11 randomized clinical trials, involving a total of 2,200 subjects (including 330 children), showed that patients belonging to the *S. boulardii* group are likely to achieve *H. pylori* eradication (79.6% instead of 71% observed patients in the control group) and less likely to experience any therapy-related adverse effects, especially diarrhea and nausea.36 The authors conclude, however, that despite a significant increase in the eradication rate, it is still unsatisfactory.

It should be noted at this point that the application of probiotics for *H. pylori* eradication is a developing and interesting topic, which, however, requires further investigation.

**Periodontal therapy**

Numerous tests proved the presence of *H. pylori* in the oral cavity. Periodontal therapy combined with eradication brought a higher healing rate and a lower probability of recurrence. Due to the limited number and quality of this research, more extensive research is necessary.37

**Portion of vegetables**

Sulforaphane is a sulfur-containing organic substance that enhances the removal of toxic substances from the body and has an anticancer effect.38 In nature, it is found primarily in vegetables, such as Brussels sprouts, kale, kohlrabi, rucola, and cauliflower, while the largest quantities are found in broccoli. It has been proven that eating broccoli sprouts can inhibit the growth of *H. pylori*.39 The such studies was carried out on a small group of respondents and does not provide strong evidence, but shows possible treatment options or treatment support.

**Summary**

Reviewing the history of discoveries and treatments of *H. pylori*, one can see the great impact of this bacterium on gastrointestinal disorders. Detection of *H. pylori* and its eradication facilitate the treatment of chronic gastritis, gastric mucosal erosion, gastric and duodenal ulcers, stomach cancer, MALT lymphoma as well as unexplained iron-deficiency anemia, idiopathic thrombocytopenia, and vitamin B12 deficiency. The indications regarding the eradication have changed, especially those concerning bismuth. The first therapies were based on this element, and then it was replaced with PPIs in 2000. In the following years, the same efficacy of treatment regimen based on bismuth and PPIs was proven, so bismuth was again used in the therapy. The main problem of eradication failure is the increasing resistance of bacteria to antibiotics. To the medicines used in recent years – apart from clarithromycin, amoxicillin and metronidazole – fluoroquinolones have been included.

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