Scientific evidence based on controlled clinical research confirm substantial benefits resulting from the eradication of *H. pylori* infection in such pathologies of the alimentary tract as: gastric peptic and duodenal ulcer (active or confirmed in the future and ulcer disease complications), MALT (Mucosa Associated Limphoid Tissue) lymphoma, atrophic gastritis, past stomach resection, gastric cancer in the family. The above group of indications is strongly recommended for eradicative treatment. During the last several years there have been many guidelines made by international and national specialist groups.

“Test and treat” strategy of undiagnosed dyspepsia treatment is based on possibility to carry out non-invasive tests confirming *H. pylori* infection. First symptoms of dyspepsia in people over 45 years of age constitute recommendation for endoscopy, as well as symptoms assumed to be “alarming” (loss of weight, anaemia, bloody vomiting, tarry stool, dysphagia) regardless of patient age. An individual approach to eradication is proposed in gastroesophageal reflux disease, and use of non-steroid anti-inflammatory drugs.

Antibacterial activity towards *H. pylori* is shown by many antibiotics (amoxicillin, macrolides, tetracyclines) and some other chemotherapeutic agents (nitroimidazoles) and bismuth. PPIs are recommended, because through increase of pH in stomach they create conditions to act for antibiotics. During the stage of first line triple therapy, it is advised to apply PPI and two antibacterial medicines at the same time (PPI + amoxicillin+metronidazole or clarithromycin). Such therapeutic action ensures achievement of eradication of *H. pylori* infection in 80-90% of cases. In case of lack of treatment efficiency in the first-line therapy, 7-14 day treatment may be repeated using triple therapies (PPI + 2 antibiotics) substituting the antibiotic with the metronidazole or tetracycline, or quadruple therapies (PPI + bismuth citrate + 2 antibiotics). Side effects during eradicative treatments occur quite rarely (from 15 to 30%).
Indications for treatment of Helicobacter pylori infection

The proved causal links between Helicobacter pylori (H. pylori) infection and the gastric and duodenum diseases (ulcer disease, MALT lymphoma, gastric cancer of intestine type) in an obvious way led to tests of possibilities to eradicate the infection, thus to casual treatment and prevention of such diseases. Whom and how should we treat? During the last several years there have been many agreements (consensuses) made by international and national specialist groups (1-3) also in Poland (4). The guidelines were, moreover, prepared for special population groups (children) (5) and for doctors in the general medical practice (6). The most recent versions of European and Polish consensus constitute the basis of this presentation (1, 4). Scientific evidence based on controlled clinical research confirms substantial benefits resulting from the eradication of H. pylori infection in such pathologies of the alimentary tract as: gastric and duodenal ulcer (active or confirmed in the future and ulcer disease complications), MALT (Mucosa Associated Limphoid Tissue) lymphoma, atrophic gastritis, past stomach resection, gastric cancer in the family (I degree of relationship). The above group of indications is strongly recommended for eradicative treatment in both European and Polish consensus (Table 1). Those indications were supplemented with treatment, upon the patient’s request and after medical consultation, of people with H. pylori infection without clinical symptoms. Possible side effects related to the treatment were also presented.

Not in all cases of diseases co-existing with H. pylori infection it was explicitly stated that eradication of H. pylori was to be the basic element of their treatment. It particularly concerns non-ulcer dyspepsia (7, 8) and use of non-steroid anti-inflammatory drugs (NSAIDs) (9). In order to avoid controversies in everyday practice, the Polish Helicobacter pylori Working Group proposed to include those situations in recommendations for H. pylori infection treatment with individual action tactics. Similarly, an individual approach to eradication is proposed in gastroesophageal reflux disease (10, 11).

In the Polish consensus 2004, it was proposed to differentiate the tactics in H. pylori infection treatment at the level of basic health care and at the level of gastroenterologist (or oncologist). It was advised that some diseases which

Table 1. Recommendations for H. pylori infection treatment (European (Maastricht –3 2005) and Polish consensus 2004

- Gastric and duodenal ulcer (active or confirmed in the past and ulcer disease complications)
- MALT lymphoma
- Atrophic gastritis
- Past gastric resection
- Gastric cancer in the family (I degree of relationship*)
- Upon the request of the patient (after consultation)

* In the Polish consensus, due to high incidence of gastric cancer in Poland, it was recommended to implement eradicative treatment also in the II degree relationship.
require highly specialized knowledge and experience, as well as appropriate
diagnostic base should be treated in regional gastroenterological or oncological
centers because in some cases (e.g. MALT lymphoma) eradication of *H. pylori*
infection is only one element of a complex treatment of these diseases. The list of
diseases which should be treated in the specialist health care is included in *Table 2*. Treatment of the specified diseases in basic health care may put the ill person
at risk of delay in implementation of appropriate diagnostics and treatment.

*Eradication in case of patients with dyspepsia symptoms. “Test and treat” strategy*

How to treat a patient who comes first time to general practitioner due to
unusual dyspeptic symptoms (undiagnosed dyspepsia)? The recommended
algorithm is presented in *Fig. 1*.

*Table 2. Recommendations for treatment in specialist (gastroenterological or oncological) health
care (Polish Consensus 2004)*

- MALT gastric lymphoma
- Menétrier disease
- Precancerous lesions (multifocal atrophic lesions, metaplasia, dysplasia)
- Gastric resection due to early cancer
- Adenomatous and hyperplastic gastric polyps (after their removal)
- Lack of *H. pylori* infection eradication after second attempt of treatment
- Clinical situation raising doubts

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**Algorithm of diagnostics and treatment of undiagnosed dyspepsia**

1. **Undiagnosed dyspepsia**
   - **Age > 45 years or alarming symptoms**
     - **Gastroscopy**
     - **Gastrological consultation**
   - **Age < 45 years without alarming symptoms**
     - **Non-invasive test for *Helicobacter pylori* infection**
     - (+) **Eradicative treatment**
     - (-) **H₂RA, PPI treatment**

*Fig. 1. Algorithm of diagnostic and therapeutic procedure in undiagnosed dyspepsia*
In some cases the symptoms of dyspepsia may be related to serious organic
diseases (ulcer disease, cancer). In such situations many people, without medical
consultation, take medications strongly inhibiting gastric secretion (blocking H₂
receptor, Proton Pump Inhibitor - PPI). In both consensuses (Maastricht-3 2005,
Polish 2004) it was accepted that due to a low cancer risk in people under 45 there
is no need to carry out endoscopy in that patient group. In more than 60% of
people no inappropriate symptoms are found during endoscopy (functional
dyspepsia). From the above group only those patients should be selected, who
show symptoms typical for pyrosis because in such cases a separate strategy
should be applied (12).

First symptoms of dyspepsia in people over 45 constitute recommendation for
endoscopy (diagnosed dyspepsia), as well as symptoms assumed to be “alarming”
(loss of weight, anaemia, bloody vomiting, tarry stool, dysphagia) regardless of
patient age.

“Test and treat” strategy of undiagnosed dyspepsia treatment is based on
possibility to carry out non-invasive tests confirming *H. pylori* infection. Firstly,
it is recommended to carry out a breathing test with the urea marked ¹³C (UBT
¹³C) or marking *H. pylori* antigen in the stool, or carrying out laboratory serologic
tests. European recommendations do not suggest to start treatment only on the
grounds of positive results of tests based on marking anti-*H. pylori* antibodies in
saliva or urine (“near-patient tests”) (1). In Polish conditions the above remark
concerns tests available at pharmacies and carried out by patients themselves.

Despite the fact that direct impact of *H. pylori* infection eradication on
regression of dyspepsia symptoms is still doubtful (13, 14), this treatment is
beneficial for those patients (prevention or treatment of gastric ulcers; in persons
*H. pylori* negative the ulcer disease may be excluded as a cause of complaints;
selection of patients for endoscopy increases the availability of this test for other
recommendations) (15).

Polish consensus (4), due to a limited availability in Poland of non-invasive
tests which confirm *H. pylori* infection, recommended slightly different actions.
In the case of first medical visit of patient under 45, with the symptoms of
dyspepsia but without alarming symptoms, the empirical treatment was suggested
with application of medicines inhibiting hydrochloric acid, prokinetics or alkali
descretion. If there is no improvement or if dyspepsia symptoms recur, it was
recommended to act in accordance with the European recommendations (1).

**NSAIDs use and eradication of *H. pylori* infection**

*H. pylori* infection and NSAIDs are independent factors leading to
occurrence of peptic or duodenum ulcers (9). However, both of them act
synergically when they occur simultaneously. Single tests indicate that *H. pylori*
eradication reduces the frequency of complications (including bleeding) in
stomach and duodenum caused by intake of NSAID (16), and acts preventively
before planned long-term treatment with those medicines (17). There are no objective clinical data concerning side effects of inhibitors of Cyclooxygenase-2 and \textit{H. pylori} infection. The European Consensus (Maastricht-3 2005) and Polish recommendations suggest eradication of \textit{H. pylori} infection before planned long-term NSAID treatment. Moreover, the European Consensus recommends eradication of \textit{H. pylori}: (a) in persons who use NSAID occasionally, (b) and those using aspirin for a long time after the incident of bleeding of the alimentary tract (1).

\textit{Gastroesophageal reflux disease (GORD) and H. pylori infection}

Our present knowledge allows for the statement that \textit{H. pylori} infection is not a causative factor of GORD. Some earlier publications suggested that \textit{H. pylori} infection might have negative impact on GORD symptoms because eradication in case of some patients strengthens or causes occurrence of reflux symptoms (18, 19). The majority of patients with GORD, \textit{H. pylori} – positive, suffer from predominant-corpus gastritis, even though some data suggest that it concerns only Afro-Asian population, while European and North American population in a lower degree (20). Eradication in case of those patients may cause increase of acid secretion through regression of inflammation, reducing at the same time the atrophy of mucous membrane (21). A positive influence of the intestinal metaplasia has not been proved yet. Due to the fact that deep suppression of secretion with PPI may increase , the European and Polish Consensus suggests eradication of \textit{H. pylori} infection in case of planned long-term treatment with PPI of the patients with GORD. However, they do not recommend routine tests of \textit{H. pylori} status and eradication of the infection in all patients with this disease.

\textit{Diseases outside the alimentary canal and H. pylori infection}

The European Consensus Maastricht-3 2005 pays attention to possible connection between \textit{H. pylori} infection and essential thrombocytopenia and anemia caused by the iron deficiency in people without ulcer disease and recommends eradication in those cases (1).

\textit{Lack of indications for eradication}

In the European Consensus Maastricht-3 2005 there were no clinical situations distinguished in which eradication was not recommended. It may only be concluded that it is not recommended to carry out diagnostics and treatment of persons without clinical symptoms routinely (indication for treatment upon patient request).

In the Polish Consensus 2004 it was established that there were no indications to implement treatment of \textit{H. pylori} infection: (a) in persons without the clinical symptoms (and without risk factors of gastric cancer), (b) in gastroesophageal
reflux disease, (c) in persons treated with NSAIDs (except for planned long-term treatment), (d) in cases of chronic superficial gastritis, (e) in diseases outside the alimentary tract. Due to the new facts discussed above, clinical situations, except for point “a”, require a revision. The Polish Consensus 2004 does not recommend treatment of persons with substantiated *H. pylori* infection without clinical symptoms and without gastric cancer risk factors. Those persons may be treated upon their request after having received information on possible negative effects of eradicative treatment (side effects).

*Recommended methods of treatment of H. pylori infection*

Antibacterial activity towards *H. pylori* is shown by many antibiotics (amoxicillin, macrolides, tetracycline) (22) and some other chemotherapeutic agents (nitroimidazoles) (23). However, a therapeutic effect (eradication) in application of a single medicine does not exceed 40%. Important antibacterial effect against *H. pylori* is also shown by bismuth salts (24). On the basis of a great number of tests, it was shown that the most effective therapeutic system, which gives the largest percentage of *H. pylori* infection eradication, consists of simultaneous application of PPI and two antibiotics or a chemotherapeutic agent – metronidazole (25), or bismuth salts.

Among the medications that reduce gastric secretion, PPIs are recommended, because through increase of pH in stomach they create better conditions for antibiotics to act and may cause healing of existing ulcer. Effect of the H$_2$ receptor antagonists (H$_2$RA) is less effective in this respect and is not recommended by the Polish Consensus 2000. Some tests are being carried out on application of ranitidine bismuth citrate (mix of ranitidine with colloidal bismuth). However, tests of this medication in Europe are not sufficient, and the drug is not available on Polish market. The European Consensus Maastricht 3 2005 and the Polish Consensus 2004 do not currently recommend this medicine for *H. pylori* infection eradication.

**RECOMMENDED MEDICINES FOR TREATMENT OF H. PYLORI INFECTION**

*Medicines inhibiting secretion of hydrogen ions in stomach:*

- PPIs: omeprazole (20 mg) twice a day, lansoprazole (30 mg) twice a day, pantoprazole (40 mg) twice a day.

*Antibiotics and chemotherapeutic agents*

- Betalactams: amoxicillin (1000 mg) twice a day
- Macrolides: clarithromycin (500 mg) twice a day
- Nitroimidazoles: metronidazole (500 mg) twice a day, tinidazole (500 mg) twice a day
Bismuth salts

Bismuth citrate (120 mg) 4 times a day

In selection of chemotherapeutic agents it is important to know the frequency of occurrence of primary resistance to antibiotics of *H. pylori* strains in a given country. Primary resistance of *H. pylori* strains to metronidazole in Western Europe amounts to 7-50%, in Poland 48%. In our country the primary resistance to clarithromycin of the *H. pylori* strains is systematically increasing and amounts to 15% in children population and to 28% in general population (26). It is interesting that often primary resistance to clarithromycin of the *H. pylori* strains is accompanied by resistance to metronizidole and clarithromycin, amounting to 20% in Poland. Primary resistance of *H. pylori* to amoxicillin in Poland has not been established so far and all the strains tested were sensitive to tetracycline (26).

During the stage of first line triple therapy, it is advised to apply PPI and two antibacterial medicines at the same time in the doses indicated above. The Polish Working Group, in accordance with the European Consensus (Maastricht-3 2005), recommends 7 or 14 day long therapy. The 14 day long treatment shows slightly higher efficiency of eradication. Therapy extended to 14 days is recommended in case of failure of the first-line therapy (second-line therapy).

Taking into consideration the frequency of occurrence of primary resistance to metronidazole (48 %) and clarithromycin (about 28%) of *H. pylori* strains in Poland, the following patterns of 7 or 14 day course treatment is recommended:

- PPI + amoxicillin - 1000 mg twice a day
  + clarithromycin - 500 mg twice a day
- PPI + clarithromycin - 500 mg twice a day
  + metronidazole - 500 mg twice a day
- PPI + amoxicillin - 1000 mg twice a day
  + metronidazole - 500 mg twice a day

Due to the presence in Poland of *H. pylori* strains highly resistant to metronidazole and in some patients to clarithromycin, it is not advisable in the first-line to use therapeutic systems containing both clarithromycin and metronidazole. The Polish Consensus 2004 recommends to select for the first-line therapy the pattern containing amoxicillin and clarithromycin or amoxicillin and metronidazole. The European Consensus Maastricht-3 2005 draws attention to the fact that resistance to clarithromycin above 20% in the population seems to prefer therapeutic arrangement which in the first-line consists of: PPI + amoxicillin+metronidazole. Such therapeutic action ensures achievement of eradication of *H. pylori* infection in 80-90% of cases.

Other tactics are required in case of people with bleeding from the ulcer. Cases studied in recent years confirmed that for patients with bleeding ulcer treated not just with PPI, but with PPI being a part of eradication set, a worse direct haemostatic effect from the bleeding vessel should be expected after eradication. Thus, the Polish Consensus 2004 recommends that eradicative treatment should
be postponed, after bleeding has been controlled, when the patient starts oral feeding or after ulcer healing (usually after 10-14 days of PPI usage).

**Evaluation of the efficiency of eradicative treatment**

Evaluation of eradication efficiency should take place after 4-6 weeks from the termination of the treatment on the basis of the breathing test or *H. pylori* antigen examination in faeces (if available) or rapid non-invasive test or histologic test, or both (if endoscopy is to be carried out). Serologic test are not useful for evaluation of eradication.

There is no need to evaluate the efficiency of eradication in all treated patients. However, it is absolutely necessary (with endoscopy control) in case of peptic ulcer, as well as in patients with bleeding from duodenal ulcer, in those with complications resulting from ulcer disease in their medical history if there is no clinical improvement after the treatment, and in patients with MALT gastric lymphoma and Menetrier disease.

In case of lack of treatment efficiency in the first-line therapy, 7-14 day treatment may be repeated using triple therapies (PPI + 2 antibiotics) substituting the antibiotic with the metronidazole (500 mg three times a day) or tetracycline (500 mg four times a day), or quadruple therapies (PPI + bismuth citrate + 2 antibiotics). If in the first-line therapy clarithromycin was used, it is recommended to use metronidazole in the second-line therapy, or the other way round. If there is no improvement after treatment in the second-line therapy and there are absolute recommendations for eradication, the patient should be directed to a specialist center, in order to carry out bacteriological culture and to check of the strain resistance to antibiotics. At that point the diagnostics should be focused on other causes of the ulcer, such as: lymphoma, Zollinger-Ellison syndrome, Crohn disease or use of NSAID by the patient.

There are no definite opinions whether medicines inhibiting the gastric secretion should still be used after the eradicative treatment in case of people with ulcer disease. It is commonly stated that in the majority of duodenal ulcer cases there is no such necessity. In case of serious ulceration or bleeding the prolonged treatment with medicines inhibiting gastric secretion (PPI or H₂RA) is recommended for the subsequent 3-4 weeks. The Polish Consensus 2004 recommends longer treatment for all patients because the lack of eradication of *H. pylori* in 10-15% of patients has to be considered, which may put them at risk of ulcer complications or maintenance of clinical symptoms of the disease.

**Recommended action in case of *H. pylori* in children**

This issue is of a special importance because the age of a child when the infection occurs is of great significance for the further progress of the alimentary tract diseases in the later period. The Polish Working Group, while analyzing this issue, took into account the paediatric consensus of 1998, prepared by the
European Pediatric Helicobacter Pylori Study Group (5) and the Helicobacter pylori Working Group of the European Society of Gastroenterology, Hepathology and Children Nutrition (6). The main arrangements resulting from those studies are presented below:

1. H. pylori in children causes chronic gastritis, eradication of the infection leads to removal of inflammatory lesions.

2. H. pylori is linked with the ulcer disease in children; eradication of the infection limits recurrence of the ulcer disease.

3. So far, it has not been proved that chronic gastritis is a cause of chronic stomach ache in children or of dyspepsia symptoms, except for cases where the ulcer disease coexists.

4. So far it has not been proved that infection eradication leads to removal of painful complaints in children with the chronic gastritis. Therefore, it is not recommended to carry out screening examinations for possible infection in case of children with dyspepsia symptoms.

5. Tests for H. pylori infection in children should be carried out only when the symptoms suggest the existence of organic disease and they are serious enough to justify the risk of anti-bacterial treatment.

6. The recommended diagnostic treatment for children with upper part of alimentary canal symptoms, suggesting innate base, is endoscopy with collection of specimen for histological and bacteriological examinations.

7. Confirmation of the infection is the indication for application of eradicative treatment.

8. The treatment result should be monitored with reliable non-invasive tests.

9. Serologic test are not reliable in case of children.

10. Urea breathing test with carbon $^{13}$C is an extremely reliable test for older children, but its usefulness for children below 2 requires further research.

In the Polish Consensus 2004 it was established that the only certain indications for eradication in children and youth up to 14 years old are those specified in Table 3.

Despite the lack of well documented research concerning treatment of H. pylori infection in children, the Polish Consensus recommended to apply the same set of medicines as for adults for 7 days.

Below there are the dosages recommended by the Polish Consensus 2004 for children and youth below 14 years old for medicines used in H. pylori infection eradication in case of a 7-day treatment.

Omeprazole - (0.5 mg/kg/day in one or two dosages, maximum twice 20mg/day)

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<th>Table 3. Indications for eradication in children and youth up to 14 years old</th>
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<td>• Gastric and duodenal ulcer</td>
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<td>• Chronic gastritis</td>
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Bismuth citrate - (8 mg/kg/day in two to four dosages, maximum twice 240mg/day)
Amoxicillin - (40-50 mg/kg/day in two or three dosages, maximum twice 1000 mg/day)
Clarithromycin - (15 mg/kg/day in two dosages, maximum twice 500 mg/day)
Metronidazole or tinidazole - (20 mg/kg/day in two dosages, maximum twice 500 mg/day)

Side effects linked with H. pylori infection treatment

Treatment, in particular so complex as in H. pylori infection, should be safe. The aims of the treatment, i.e. eradication of H. pylori and cure of the disease related to the H. pylori should not be combined with non-steroid anti-inflammatory drugs and this represents clinically important problem due to possible side effects.

Side effects during eradicative treatments occur quite rarely (from 15 to 30%). They are the following: dyspepsia (1-15%), nausea (3-10%), vomiting (1,5-4%), abdominal pain (1-3%) and diarrhoea (4-8%). Moreover, a possibility of development of pseudomembranous enteritis caused by Clostridium difficile (about 1%) has to be considered. Eradication of H. pylori in some patients may cause the occurrence of symptoms, previously absent, of gastroesophageal reflux disease with erosive esophagitis. Furthermore, one has to consider the increase of acquired resistance of bacteria to the antibiotics of those micro-organisms which cause infections outside the alimentary canal, which may make it difficult to treat other diseases in future.

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