Does *Helicobacter pylori* infection influence the incidence of acid gastroesophageal reflux in children and teenagers?

Czy zakażenie *Helicobacter pylori* wpływa na częstość występowania kwaśnego refluksu żołądkowo-przełykowego u dzieci i młodzieży?

Monika Parzęcka, Anna Szaflarska-Popławska, Grażyna Mierzwa

Chair and Department of Paediatrics, Allergology and Gastroenterology, Ludwik Rydygier *Collegium Medicum,* Bydgoszcz, Nicolaus Copernicus University, Toruń

Przegląd Gastroenterologiczny 2009; 4 (3): 159–165

Key words: *Helicobacter pylori* infection, acid gastroesophageal reflux.
Słowa kluczowe: zakażenie *Helicobacter pylori*, kwaśny refluks żołądkowo-przełykowy.

Address for correspondence: Monika Parzęcka, MD, Chair and Department of Paediatrics, Allergology and Gastroenterology, Ludwik Rydygier *Collegium Medicum,* Bydgoszcz, Nicolaus Copernicus University, Toruń, 9 Maria Skłodowska-Curie St, 85-094 Bydgoszcz, phone +48 52 585 48 50, fax +48 52 585 40 86, e-mail: klped@cm.umk.pl

Abstract

Introduction: The role of *Helicobacter pylori* infection in pathogenesis and gastroesophageal reflux disease (GERD) incidence still remains unexplained. *Helicobacter pylori* influences the incidence of acid gastroesophageal reflux depending on the region of inflammation, concomitant inflammatory lesions of the stomach cardia and the oesophagus, bacterial virulence and motor disturbances of the gastrointestinal tract.

Aim: The aim of the study is to attempt to answer the question whether *H. pylori* infection influences acid GERD incidence in children and teenagers and also whether these dependences are connected with mucosal inflammation of the stomach cardia and the oesophagus.

Material and methods: Two hundred fourteen patients, older than 3 years of age, with dyspeptic symptoms, were included in the study. All children underwent both endoscopic examination of the upper part of the gastrointestinal tract and pH-metry. *Helicobacter pylori* infection was diagnosed on the basis of presence of the bacteria in a biopsy specimen of the mucosa and/or abnormal result of urease test and urea respiratory test.

Results: *Helicobacter pylori* infection was diagnosed in 101 patients [group I (n = 101)]. pH-metry result was abnormal in 50 patients in this group [group Ia (n = 50)], but in 51 persons the reflux index was below 4% [group Ib (n = 51)]. One hundred and thirteen patients were qualified into group II (n = 113) with excluded *H. pylori* infection. Gastroesophageal reflux was diagnosed in 56 patients from this group [group IIa (n = 56)], but was excluded in 57 cases [group IIb (n = 57)]. There was no difference concerning GERD incidence (%) in compared groups (p = 0.99, *ns*). Macroscopic inflammatory lesions of the oesophageal mucosa were found in 13 patients in the group of patients with *H. pylori* infection (group I) 13/101 (12.8%) and in 11 patients without infection

Streszczenie

Wprowadzenie: Nadal niewyjaśniona jest rola zakażenia *Helicobacter pylori* w patogenezie i częstości występowania choroby refluksowej przełyku. Wpływ zakażenia *H. pylori* na częstość występowania kwaśnego refluksu żołądkowo-przełykowego zależy od miejsca toczącego się procesu zapalnego, współwystępowania zmian zapalnych błony śluzowej wpustu żołądka i przełyku, wirulencji bakterii oraz występowania zaburzeń motorycznych przewodu pokarmowego.

Cel: Celem pracy była próba odpowiedzi na pytania, czy zakażenie *H. pylori* wiąże się z częstością występowania kwaśnego refluksu żołądkowo-przełykowego u dzieci i młodzieży oraz czy na te zależności ma wpływ zapalenie błony śluzowej wpustu żołądka i przełyku.

Materiał i metody: Badaniem objęto 214 pacjentów powyżej 3. roku życia z objawami dyspeptycznymi, u których wykonano badania endoskopowe górnego odcinka przewodu pokarmowego oraz pH-metryczne przełyku. Zakażenie *H. pylori* potwierdzano w badaniu histopatologicznym i/lub w teście ureazowym oraz mocznikowym teście oddechowym.

Wyniki: Wśród badanych było 101 pacjentów, u których stwierdzono zakażenie *H. pylori* [grupa I (n = 101)]. W 50 przypadkach wynik badania pH-metrycznego w tej grupie okazał się nieprawidłowy [grupa Ia (n = 50)], a u 51 pacjentów *indeks refluksowy* był poniżej 4% [grupa Ib (n = 51)]. Do grupy II zakwalifikowano 113 pacjentów (n = 113), u których wykluczono zakażenie *H. pylori*. W tej grupie u 56 pacjentów rozpoznano kwaśny refluks żołądkowo-przełykowy [grupa IIa (n = 56)], w 57 przypadkach wykluczono tę chorobę [grupa IIb (n = 57)]. Nie zaobserwowano różnicy między częstością (%) występowania tego schorzenia w porównywanych grupach (p = 0,99, *ns*). Makroskopowe zmiany zapalne błony śluzowej przełyku odnotowano u 13 pacjentów w grupie pacjentów

(group II) 11/113 (9.7%). The difference was not statistically significant (p = 0.47, *ns*). Only 3 patients presented inflammation of the cardia mucosa.

Conclusions:

1. *Helicobacter pylori* infection did not influence GERD incidence in children and teenagers.
2. Occurrence of inflammatory changes of the oesophageal mucosa was not dependent on *H. pylori* infection and GERD prevalence.

z zakażeniem *H. pylori* (grupa I) [13 z 101 (12,8%)] oraz u 11 osób bez zakażenia (grupa II) [11/113 (9,7%)]. Różnica nie była istotna statystycznie (p = 0,47, *ns*). Zapalenie błony śluzowej wpustu stwierdzono tylko u 3 pacjentów.

Wnioski:

1. Zakażenie *H. pylori* nie wpływało na częstość występowania GERD u dzieci i młodzieży.
2. Występowanie zmian zapalnych błony śluzowej przełyku nie było zależne od zakażenia *H. pylori* i występowania GERD.

Introduction

The role of *Helicobacter pylori* infection in pathogenesis and incidence of gastroesophageal reflux disease (GERD) still remains unexplained. The presence of bacteria in the stomach mucosa can be a protective and aggressive factor in relation to gastroesophageal reflux. It seems that the influence of *H. pylori* infection on incidence of acid gastroesophageal reflux depends on inflammation region and inflammation intensity [1-5], concomitant inflammatory lesions of the cardia [4, 6, 7], the stomach and the oesophagus [8], bacterial virulence [2, 9] and motor disturbances of the gastrointestinal tract that accompany infection [10-12]. The pathomechanism of these dependences is not completely known. Many reports indicate the role of nitric oxide [1, 13] and ghrelin [14] in pathophysiology concerning dependence of *H. pylori* infection and gastroesophageal reflux disease.

Aim

The aim of the study is to attempt to answer the question whether *H. pylori* infection influences acid GERD incidence in children and teenagers and also whether these dependences are connected with mucosal inflammation of the stomach cardia and the oesophagus.

Material and methods

Patients older than 3 years of age, with dyspeptic symptoms and suspected inflammation of the stomach and duodenal mucosa, were included in the study.

Exclusion criteria from the study were:

- previous diagnosis of *H. pylori* infection and its treatment,
- previous GERD diagnosis and its treatment [neutralizing drugs, proton pump inhibitors (PPI), H2-blockers],
- actual or applied till 4 weeks before antibiotic therapy,
- actual or applied till 2 weeks before therapy with proton pump inhibitors or H2-blockers.

Patients were divided into the following groups:

I) patients with dyspeptic symptoms and with mucosal inflammation of the stomach and/or the duodenum with concomitant *H. pylori* infection (n = 101):
   - Ia) patients with *H. pylori* infection and with GERD (n = 50),
   - Ib) patients with *H. pylori* infection and without GERD (n = 51);
II) patients with dyspeptic symptoms without *H. pylori* infection (n = 113):
   - IIa) patients without *H. pylori* infection and with GERD (n = 56),
   - IIb) patients without *H. pylori* infection and without GERD (n = 57).

All patients underwent endoscopic examination of the upper part of the gastrointestinal tract. The following biopsy specimens were taken: three biopsy specimens of the gastric mucosa from the prepyloric region (one for urease test, one for histological examination, one for *H. pylori* identification with PCR method), from the stomach fundus or from the upper part of the stomach body, and from unexplained macroscopic lesions. Macroscopic lesions within mucosa of the oesophagus, the stomach and the duodenum were assessed during examination according to Sydney System classification. Biopsy specimens for histopathological examination were stained with haematoxylin and eosin to assess inflammation. Giemsa method modified by Gray was used to identify *H. pylori* bacterium. The whole picture was assessed according to Sydney System classification.

Urease test was performed in every patient. Confirmation or exclusion of *H. pylori* infection was also obtained, performing the urea respiratory test in patients. ^{13}C concentration was measured with the analyser of infra-red radiation OLYMPUS Fanci 2, assuming 4‰ as the cut-off point.

pH-metry of the oesophagus was used in all patients to assess exposure of the oesophageal mucosa to gastric contents. Additionally, all patients before placing the probe underwent endoscopic examination of the upper gastrointestinal tract and the level of the stomach cardia was defined. A reference electrode was glued to the skin of the chest.

Preparation for the study:

- at least 6 h fasting to ensure stomach is empty, important because of possible vomiting reflex during the probe placement; food can also neutralize

the stomach pH, impeding localization of the probe placement (for example too deep electrode placement in the stomach),
- cessation of application of drugs that change the stomach pH or influence motor activity of the gastrointestinal tract for at least 7 days.

The examination was performed for at least 18 h and always contained a period of night-time sleep. Maximum time of examination was 23 h and 44 min, mean time of examination was 22 h and 12 min.

Total percent of pH duration below 4, called the reflux index, exceeded 4% and was assumed in this report as the presence of pathological acid GERD.

Test for two fractions was used in statistical analysis. Abnormal result of pH-metry (reflux index > 4%) was acknowledged as a criterion of GERD diagnosis. *Helicobacter pylori* infection was diagnosed in patients with a positive result of the urease test and/or abnormal result of the urea breath test and also with presence of the bacteria in biopsy specimens of gastric and/or duodenal mucosa. A confidence level of 0.05 was regarded as reliable to verify hypotheses. Values of $p > 0.05$ were regarded as absence of a significant difference between analysed features (*ns – not significant*).

Agreement of the Bioethical Committee of Ludwik Rydygier Memorial *Collegium Medicum* in Bydgoszcz was obtained to perform the study.

Results

Two hundred fourteen children aged from 5 to 18 years were included in the study (mean 13.2 ±3.09). Mean age was 13.4 ±3.07 in the group of patients with inflammation of gastric and/or duodenal mucosa with concomitant *H. pylori* infection, but in the control group without *H. pylori* infection was 13.1 ±3.1.

There were 101 patients among all those analysed in whom *H. pylori* infection was diagnosed (group I). In 50 cases the pH-metry result was abnormal in this group (group Ia), and in 51 patients the reflux index was below 4% (group Ib). One hundred thirteen patients with excluded *H. pylori* infection were qualified into group II. Gastroesophageal reflux (group IIa) was diagnosed in 56 patients in this group, but in 57 cases GERD was excluded (group II).

There was no difference between GERD incidence (%) in the group of patients with inflammation of gastric and/or duodenal mucosa with concomitant *H. pylori* infection in comparison with the group without *H. pylori* infection. Precise data of this analysis are shown in Table I.

Macroscopic inflammatory lesions in the oesophagus were noted in 13 patients in the group with *H. pylori* infection (group I) [13/101 (12.8%)] and in 11 patients without infection (group II) [11/113 (9.7%)].

Table I. Results of analysis concerning GERD incidence in the group of patients with inflammation of gastric and duodenal mucosa with concomitant *H. pylori* infection and in the group without *H. pylori* infection

Tabela I. *Wyniki analizy częstości występowania GERD w grupie pacjentów z zapaleniem błony śluzowej żołądka i dwunastnicy ze współistniejącym zakażeniem H. pylori oraz w grupie bez zakażenia H. pylori*

Group	GERD	Percent of patients with GERD	Test for 2 fractions	
			u	*p*
I	50	49.5	0.008	0.99 (*ns*)
II	56	49.6		

Table II. Results of analysis concerning incidence of oesophagitis

Tabela II. *Wyniki analizy występowania zapalenia przełyku*

Group	Oesophagitis	Percent of patients with oesophagitis	Test for 2 fractions	
			u	*p*
I	13	12.9	0.73	0.45 (*ns*)
II	11	9.7		

The difference was not statistically significant. Precise data of this analysis are shown in Table II.

Histopathological confirmation of cardia inflammation was performed in 3 patients from group I (3/101), but then *H. pylori* presence in the cardia region was found in one patient (1/3). All patients revealed cardia inflammation together with GERD. This dependence was not analysed statistically.

Discussion

Helicobacter pylori infection and delayed stomach emptying are gastric factors influencing GERD [2, 4, 13]. The role of *H. pylori* in pathogenesis of gastroesophageal reflux disease and interdependence of these pathologies still remain controversial.

Helicobacter pylori's influence on gastroesophageal reflux disease can happen in different manners. They include the following processes:
- influence on gastric acid production,
- inflammation induction in the gastric cardia,
- induction of nitrogen oxide production,
- influence on ghrelin production.

Until quite recently it was considered that *H. pylori* eradication deteriorates the extent of gastroesophageal reflux disease because of decreased hypochlorhydria accompanying infection [15]. Changes in gastric acid production are mostly connected with infection location and the influence of infection on activity of oxyntic cells that mainly occur in the stomach fundus and stomach body. These cells are stimulated by histamine, gastrin and acetylcholine. Additionally, increase of gastrin concentration is caused by the histamine metabolite $N\alpha$-methylhistamine that is produced by *H. pylori* (Figure 1) [3].

Influence of *H. pylori* infection on frequency and degree of intensity of acid gastroesophageal reflux depends on inflammation region: gastric antrum, corpus or in the whole stomach [2].

Infection of the gastric antrum is connected with increased gastrin concentration that results in increased acidity and volume of gastric acid (oxyntic glands are mainly located in the stomach body and in the fundus) and also with acceleration of gastric emptying and decrease of lower oesophageal sphincter (LES) tension [1, 2]. Decreased tension of the LES is also observed in increased production of prostaglandins and activity of nitric oxide [1, 13]. Nitric oxide can be a neurotransmitter responsible for formation of transient lower oesophageal sphincter relaxations (TLESRs) [16].

Analyses during recent years indicate that occurrence of gastroesophageal reflux disease changes depending on geographic region and is greater in well developed countries. However, it was observed that the percentage of persons with GERD symptoms and with *H. pylori* infection is lower than in the group without infection. This may suggest a protective influence of this bacteria in relation to GERD [17]. Results of epidemiological studies indicate that there is inverse dependence between GERD and *H. pylori* infection [9, 18].

Studies of O'Connor *et al.* [19] report that incidence of *H. pylori* infection in patients with gastroesophageal reflux disease is lower than in control groups (34 vs. 50.2%). *Helicobacter pylori* infection with GERD was found in 57% of patients with symptoms suggesting GERD in the study of Gisbert *et al.* [20], but the bacteria's presence was confirmed in 52% of patients with a normal pH-metry result. That fact indicates no dependence between GERD and *H. pylori*.

Our studies revealed that *H. pylori* infection did not influence the incidence of acid gastroesophageal reflux.

An interesting relation between infection and pathogenesis of gastroesophageal reflux disease was presented in the study of Thor *et al.* [14], pointing to the role of ghrelin in this pathomechanism. Isomoto *et al.* [21] in their studies among patients with infection noticed low ghrelin levels that increase after eradication. Ghrelin increases secretion of gastric acid and has intense prokinetic activity in relation to LES and influences vagus nerve activity. These dependences can contribute to GERD formation [14].

Some researchers consider that *CagA-positive H. pylori* strains [1, 22] and inflammation of the whole stomach (pangastritis) [2] have a protective role. Protective character of *CagA-positive* strains is a result of extension and severity of induced inflammation due to the fact that severe inflammation causes significant failure of acid production [22-24].

Studies concerning 944 Norwegian patients proved that *H. pylori* infection, irrespective of *CagA* occurrence, did not influence GERD [25].

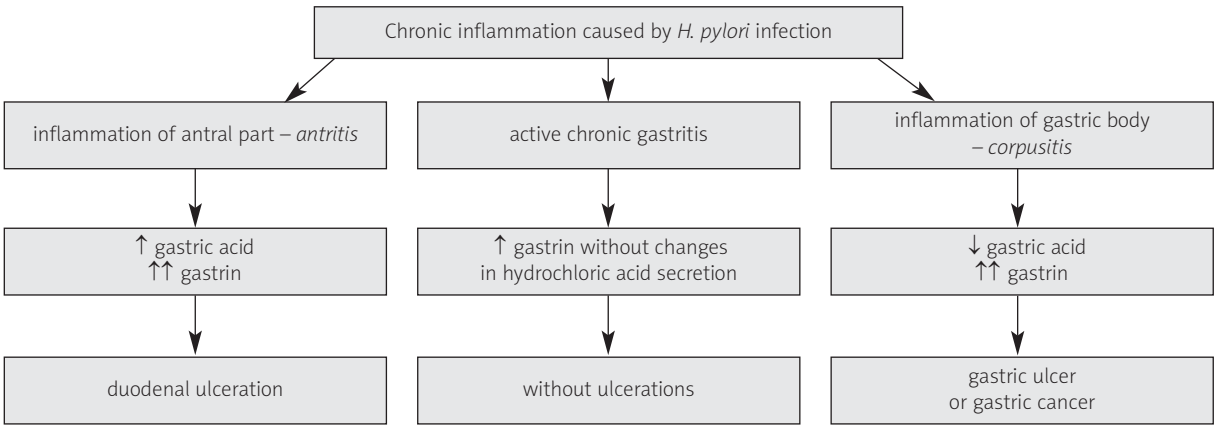

Fig. 1. Influence of *H. pylori* infection on gastric secretion
Ryc. 1. *Oddziaływanie zakażenia H. pylori na wydzielanie żołądkowe*

The pathomechanism of cardia inflammation in patients with *H. pylori* infection and with GERD can be controversial. Subcardial localization causes release of nitric oxide, inflammatory cytokines and prostaglandins that induces periodic pressure decreases within the lower oesophageal sphincter [4]. The results of many studies indicate that cardia inflammation, causing stimulation of chemokines produced locally in the mucosa, is significantly connected with infection, but not with GERD [6, 7].

The Endoscopy Group from Finland tried to find a connection between cardia inflammation and gastritis caused by *H. pylori* infection and with endoscopically proved erosive oesophagitis [24]. This study was performed among 1053 patients and cardia inflammation was found in 3/4 of cases. Sixty nine percent of patients in this group showed chronic gastritis (*H. pylori* infection was confirmed in 70% of patients). Concerning the group of patients with normal histopathological results, erosive oesophagitis was the main risk factor of cardia inflammation. *Helicobacter pylori* infection was a main risk factor of cardia inflammation in patients with chronic gastritis.

Our studies revealed only 3 patients suffering from cardia inflammation, and this fact may be connected with the young age of the studied group.

Many reports analyse the dependence of *H. pylori*'s influence in relation to the degree of oesophageal damage in GERD.

Wu *et al*. [8], in their studies in a group of 104 patients with diagnosed erosive oesophagitis graded with the Los Angeles scale, tried to assess the influence of *H. pylori* infection on oesophagitis severity. Incidence of *H. pylori* infection in symptomatic patients with oesophagitis was lower than in the control group. Age and hiatus hernia were connected with inflammation severity. *Helicobacter pylori* infection negatively correlated with oesophagitis, but did not correlate with its severity.

Almost 6000 Japanese underwent screening tests for *H. pylori* infection, gastroesophageal reflux disease and gastric cancer. On the basis of these studies it was noted that oesophagitis was diagnosed more rarely, but atrophic lesions of the gastric mucosa and gastric cancer were diagnosed more often in patients with *H. pylori* infection [26].

Anderson *et al*. [27] determined the incidence of oesophageal adenocarcinoma, Barrett oesophagus and reflux inflammation of the oesophageal mucosa depending on *H. pylori* infection in 260 patients. Simultaneously, the influence of inflammation on occurrence of atrophic lesions in the stomach was studied. *Helicobacter pylori* infection and atrophic lesions of the gastric mucosa inversely correlated with every analysed oesophagus disease.

Koine *et al*. [28] demonstrated that reflux oesophagitis occurs more often in patients without *H. pylori* infection and together with unchanged gastric secretion of hydrochloric acid.

Similar dependences were obtained in the analysis of occurrence concerning endoscopic erosive lesions within oesophageal mucosa in relation to infection among Turkish patients (n = 14 380) [29]. Shahabi *et al*. [30] emphasize the protective influence of *H. pylori* infection on GERD, using a neuroimmunological mechanism, and the bacteria's influence on sympathicotonia and activity of the vagus nerve. It can cause an effect of *H. pylori* on tension of the lower oesophageal sphincter and stimulation of the cholinergic anti-inflammatory cascade.

In turn, Tsai *et al*. [31] noticed that *H. pylori* infection insufficiently changes pH of the gastric juice, causing no protective activity concerning oesophageal mucosa.

Our studies revealed that presence of oesophagitis was independent of *H. pylori* infection and GERD. Oesophagitis in 61.5% of patients probably had a different cause than acid gastroesophageal reflux.

It is necessary to remember about oesophagitis connected with 'non-acid reflux' in analysis of reasons for oesophagitis.

pH-impedance, registering slightly acid or non-acid refluxes and acid re-refluxes, seems to be very useful in differential diagnostics of oesophagitis in children and teenagers. Our previous studies [32] show that non-acid refluxes constituted about 40% of all incidents registered by a pH-impedance probe. There are only a few reports concerning occurrence of 'non-acid refluxes' in children and teenagers. This fact is caused by difficulties in interpretation of pH-impedance results due to lack of normal values for paediatrics and problems with registering clinical symptoms.

Condino *et al*. [33] used pH-impedance in 24 children with bronchial asthma and found that 51% of registered refluxes were 'non-acid refluxes'. Reflux incidents were registered only with a pH-impedance probe in 37% of cases of dyspnoea attack.

Drugs inhibiting secretion of hydrochloric acid are applied in GERD treatment, including proton pump inhibitors (PPI), which produce an effect of inactivation of the ionic ATP-ase H^+/K^+ pump [34]. It should be remembered that prolonged PPI therapy (long-term) results in decreased acidity of gastric juice and stimulates hypergastrinaemia, and also causes atrophic lesions of the gastric mucosa. It favours infection transmission into other parts of the stomach [3, 8].

There are no indications to perform tests for *H. pylori* infection in children in whom gastroesophageal reflux was diagnosed, and these dependences still remain controversial. However, it seems reasonable to consider *H. pylori* eradication when long-term PPI therapy is planned or if these patients show atrophic lesions of the stomach [2, 35, 36].

Conclusions

1. *Helicobacter pylori* infection did not influence GERD incidence in children and teenagers.
2. Occurrence of inflammatory changes of the oesophageal mucosa was not dependent on *H. pylori* infection and GERD prevalence.

Grant for Thesis Supervisor of Ministry of Science and Informatics KBN 2PO5E 077 29.

References:

1. Bukowska L, Korzonek M, Szmatłoch E. Choroba refluksowa przełyku – problemy diagnostyki i terapii. Przegl Lek 2002; 59: 99-103.
2. Dzieniszewski J, Jarosz M. Choroba refluksowa żołądkowo-przełykowa a zakażenie Helicobacter pylori. Gastroenterol Pol 2000; 7: 119-22.
3. Konturek SJ. Żołądek i dwunastnica. In: Gastroenterologia i hepatologia kliniczna. Konturek SJ (ed.). Wydawnictwo Lekarskie PZWL, Warszawa 2001; 138-56.
4. Marek T, Nowak A, Rymarczyk G. Choroba refluksowa przełyku – wybrane zagadnienia. Przew Lek 1999; 6: 44-5.
5. Mierzwa G, Czerwionka-Szaflarska M, Bała G, et al. Choroba refluksowa u dzieci z zapaleniem błony śluzowej żołądka i (lub) dwunastnicy ze współistniejącym (lub bez) zakażeniem Helicobacter pylori. Ped Współcz 2003; 5: 17-20.
6. Goldblum JR, Richter JE, Vaezi M. Helicobacter pylori infection, not gastroesophageal reflux, is the major cause of inflammation and intestinal metaplasia of gastric cardiac mucosa. Am J Gastroenterol 2002; 97: 302-11.
7. Isomoto H, Nishi Y, Wang A, et al. Mucosal concentrations of proinflammatory cytokines and chemokines at gastric cardia: implication of Helicobacter pylori infection and gastroesophageal reflux. Am J Gastroenterol 2004; 99: 1063-8.
8. Wu CH, Wu MS, Huang SP, et al. Relationship between Helicobacter pylori infection and erosive gastroesophageal reflux disease. J Formos Med Assoc 2004; 103: 186-90.
9. Kuipers EJ, Malfertheiner P. Helicobacter pylori and nonmalignant diseases. Helicobacter 2004; 9 Suppl 1: 29-34.
10. Sładek M, Jedynak-Wąsowicz U, Pieczarkowski S, et al. Zaburzenia motoryki górnego odcinka przewodu pokarmowego dzieci z zakażeniem Helicobacter pylori. Ped Współcz 2002; 4: 335-8.
11. Toporowska-Kowalska E, Wąsowska-Królikowska K, Bodalski J, et al. Czynność mioelektryczna żołądka u dzieci z cukrzycą typu I i zakażeniem Helicobacter pylori – doniesienie wstępne. Ped Współcz 2002; 4: 347-9.
12. Wąsowska-Królikowska K, Plocek A, Toporowska-Kowalska E. Zaburzenia czynnościowe przewodu pokarmowego w alergii pokarmowej u niemowląt i małych dzieci. Ped Współcz 2004; 6: 435-8.
13. Orenstein SR. Gastroesophageal reflux. Pediatr Rev 1999; 20: 24-8.
14. Thor PJ, Błaut U. Helicobacter pylori infection in pathogenesis of gastroesophageal reflux disease. J Physiol Pharmacol 2006; 57 Suppl 3: 81-90.
15. Laine L, Sugg J. Wpływ eradykacji Helicobacter pylorii na rozwój nadżerkowego zapalenia przełyku i objawy choroby refluksowej przełyku: analiza post hoc ośmiu prospektywnych badań klinicznych ze ślepą próbą. Am J Gastrenterol 2002; 97: 2992-7.
16. Parkman HP, Fisher RS. Contributing role of motility abnormalities in the pathogenesis of gastroesophageal reflux disease. Dig Dis 1997; 15 (Suppl 1): 40-52.
17. Jarosz M. Komentarz do artyk. Helicobacter pylori a choroba refluksowa przełyku. Med Dypl 2005; 14: 120-2.
18. Cremonini F, Di Caro S, Delgado-Aros S, et al. Meta-analysis: the relationship between Helicobacter pylori infection and gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003; 18: 279-89.
19. O'Connor HJ. Helicobacter pylori and gastro-oesophageal reflux disease-clinical implications and management. Aliment Pharmacol Ther 1999; 13: 117-27.
20. Gisbert JP, de Pedro A, Losa C, et al. Helicobacter pylori and gastroesophageal reflux disease: lack of influence of infection on twenty-four-hour esophageal pH monitoring and endoscopic findings. J Clin Gastroenterol 2001; 32: 210-4.
21. Isomoto H, Ueno H, Saenko VAl. Impact of Helicobacter pylori infection on gastric and plasmaghrelin dynamics in humans. Am J Gastroenterol 2005; 100: 1711-20.
22. Schutze K. Helicobacter pylori and gasroesophageal reflux disease. Acta Med Austiaca 2000; 27: 122-5.
23. El-Serag HB, Sonnenberg A, Jamal MM, et al. Corpus gastritis is protective against reflux oesophagitis. Gut 1999; 45: 181-5.
24. Voutilainen M, Sipponen P, Mecklin JP, et al. Gastroesophageal reflux disease: prevalence, clinical, endoscopic and histopathological findings in 1,128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. Digestion 2000; 61: 16-3.
25. Nordenstedt H, Nilsson M, Johnsen R, et al. Helicobacter pylori infection and gastroesophageal reflux in a population-based study (The HUNT Study). Helicobacter 2007; 12: 16-22.
26. Yamaji Y, Mitsushima T, Ikuma H, et al. Inverse background of Helicobacter pylori antibody and pepsinogen in reflux oesophagitis compared with gastric cancer: analysis of 5732 Japanese subjects. Gut 2001; 49: 335-40.
27. Anderson LA, Murphy SJ, Johnston BT, et al. Relationship between Helicobacter pylori infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut 2008; 57: 734-9.
28. Koike T, Ohara S, Sekine H, et al. Helicobacter pylori infection prevents erosive reflux oesophagitis by decreasing gastric acid secretion. Gut 2001; 49: 330-4.
29. Unal S, Karakan T, Dogan I, et al. The influence of Helicobacter pylori infection on the prevalence of endoscopic erosive esophagitis. Helicobacter 2006; 11: 556-61.

30. Shahabi S, Rasmi Y, Jazani NH, Hassan ZM. Protective effects of Helicobacter pylori against gastroesophageal reflux disease may be due to a neuroimmunological anti-inflammatory mechanism. Immunol Cell Biol 2008; 86: 175-8.
31. Tsai SH, Chen CM, Chang CS, Chen GH. Effect of Helicobacter pylori infection on intragastric acidity in patients with reflux esophagitis. J Gastroenterol 2004; 39: 821-6.
32. Szaflarska-Popławska A, Mierzwa G, Bała G, et al. Ph-impedance monitoring value in diagnosis of gastroesophageal reflux in children and teenagers – preliminary report. Gastroenterol Pol 2007; 14: 251-5.
33. Condino AA, Sondheimer J, Pan Z, et al. Evaluation of gastroesophageal reflux in pediatric patients with asthma using impedance-pH monitoring. J Pediatr 2006; 149: 216-9.
34. Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing gastroesophageal reflux disease, and stress – related erosive syndrome. Gastroenterology 2000; 118 (2 Suppl): S9-31.
35. Nowak A, Marek T. Choroba refluksowa przełyku. Med Sci Rev Gastroenterol 2002; 1: 24-32.
36. Jaguszyn-Krynicka EK, Gajkowska A, Godlewska R. Czynniki wirulencji Helicobacter pylori. Mikrobiol Med 1999; 3: 3-13.