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PEPTIC ULCER DISEASE

Minsk BSMU 2019

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
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2-я КАФЕДРА ВНУТРЕННИХ БОЛЕЗНЕЙ

В. М. Сиденко

ГАСТРОДУОДЕНАЛЬНЫЕ ЯЗВЫ

PEPTIC ULCER DISEASE

Учебно-методическое пособие

Минск БГМУ 2019

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Представлены сведения об этиологии, патогенезе, классификации, основных клинических проявлениях, диагностике, дифференциальной диагностике, лечении и профилактике язв желудка и двенадцатиперстной кишки.

Предназначено для студентов 4-го курса медицинского факультета иностранных учащихся, обучающихся на английском языке.

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ABBREVIATIONS

BID — two times a day (on prescription)

COX — cyclooxygenase

ICD10 — International classification of diseases, 10th revision

NSAID(s) — nonsteroidal anti-inflammatory drug(s)

H. pylori — Helicobacter pylori

H_2-blockers — histamine H_2-receptor antagonists

PPI(s) — proton pump inhibitor(s)

PUD — peptic ulcer disease

QID — four times a day (on prescription)

TID — three times a day (on prescription)

MOTIVATIONAL CHARACTERISTICS OF THE TOPIC

Practical class topic: Functional dyspepsia. Chronic gastritis. Peptic ulcer disease.

Total hours: 6.

PUD is a relatively common condition and can occur at any age. Even being asymptomatic, it can be dangerous due to the complications. PUD can be fatal in case of late diagnosis and requires a lot of effort to treat. Accuracy of diagnosis, prescription of correct treatment, and prognosis of the disease depend on the skills of a doctor.

Millions of people are infected with *H. pylori*, which is currently considered the most common chronic infection in the world. In recent years, significant changes in the diagnosis of *H. pylori* infection and treatment of PUD have been achieved. After finding the infectious nature of gastric and duodenal ulcers by Barry Marshall and Robin Warren (1982), who were awarded the Nobel Prize for this research (2005), previously used treatment regimens were changed.

Antibiotics became the basis of therapy, making eradication of the microorganism and prevention of recurrences possible. The introduction of antibiotic therapy has revolutionized the clinical practice of gastroenterologists. However, it was necessary to summarize the available data on the treatment of *H. pylori* infection and create universal recommendations based on the principles of evidence-based medicine. In 1996, the European Group for the Study of *H. pylori* in Holland (Maastricht) organized and held a conference, which resulted in a consensus “Current European Concepts on the Management of *H. pylori* infection” (Maastricht I). Subsequently, as data were accumulated,

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the guidelines were updated and were formulated as new statements in the Maastricht II consensus (2000), Maastricht III (2005), Maastricht IV (revision of recommendations — 2010, full text published in 2012) and Maastricht V (revision of recommendations — 2015, full text published in 2017).

However, in recent years the management of PUD has become more challenging due to increasing antimicrobial resistance of *H. pylori* in many countries and wide use of NSAIDs. But discontinuation of NSAIDs use by some patients is infeasible. Nevertheless, in most of the cases it is possible to optimize regimens responsible for eradication of *H. pylori.*

The purpose of teaching and learning the topic consists of clinical thinking formation as well as acquisition of scientific knowledge on etiology, pathogenesis, diagnosis, differential diagnosis and principles of treatment of gastric and duodenal ulcers by students.

The teaching objectives are as follows:

– to consolidate students' knowledge in causes and mechanisms of development of gastric and duodenal ulcers;

– to learn clinical manifestations of PUD;

– to classify gastric and duodenal peptic ulcers;

– to explore laboratory and instrumental methods of examination, plan of examination in PUD;

– to systematize modern methods of diagnosis and differential diagnosis of gastric and duodenal peptic ulcers;

– to characterize principles of treatment of PUD, indications, treatment regimes, side effects of PPIs and anti-*Helicobacter* drugs.

Teaching and successful learning of the topic "Peptic ulcer disease" is carried out **on the basis** of the acquired knowledge and skills of students in the following disciplines:

– Latin: terminology;

– Human anatomy: digestive system structure and functions;

– Pathological anatomy: structural basis of PUD, characteristic of morphological changes, morphogenesis and principles of diseases classification;

– Normal physiology: principles of functioning of digestive system organs, mechanisms of their regulation and self-regulation, healthy body performance parameters;

– Pathological physiology: pathophysiology of digestive system, the reasons and basic mechanisms of development and outcomes of pathological processes in PUD, patterns of organs alteration in case of environmental factors influence, body reactivity and its role in pathology, diseases outcomes;

– Histology: microscopic structure of cells;

– Microbiology: characteristics of *H. pylori*, interaction with body cells, general principles of diagnosis;

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– Pharmacology: classification of drugs, pharmacodynamics and pharmacokinetics, mechanisms of drugs action and side effects;

– Internal medicine propaedeutics: clinical and laboratory methods of patient assessment, creating a plan of a patient examination.

Test questions from related disciplines:

1. Anatomy and physiology of the digestive system.
2. Main pathophysiological mechanisms of development of gastric and duodenal peptic ulcers.
3. Diagnostic methods for *H. pylori* infection
4. Characteristics of PPIs.

Test questions on the topic being discussed:

1. Definition of PUD.
2. The main causes and mechanisms of the development of gastric and duodenal peptic ulcers.
3. Classification and principles of diagnosis of PUD.
4. Clinical symptoms of gastric and duodenal peptic ulcers.
5. Modern resources of instrumental diagnosis of PUD.
6. The basic principles of eradication therapy of *H. pylori*.

Tasks for independent work. In preparation for the class, a student should work out an algorithm for managing a patient with PUD taking into account the characteristics of the clinical picture and the severity of the disease. This algorithm will be discussed in class. After finishing the analysis of clinical picture and diagnosis of PUD, it is advisable to interpret the results of instrumental and laboratory tests. Upon completion of the review of the topic, a student independently takes disease history, makes physical examination of the patient with PUD and formulates an initial diagnosis, prepares the plan of instrumental and laboratory examination as well as treatment recommendations. Some students report information received from the patients and demonstrate clinical check-up technique highlighting physical data that are the most important for the diagnosis of severity of the disease. Some students may present the results of their work in writing. Having finished the clinical analysis, it is advisable to proceed to test questions. At the end of the class, the teacher sums up the studied materials.

DEFINITION AND EPIDEMIOLOGY

Peptic ulcers are deep, non-healing defects or sores in gastrointestinal lining extending through the *muscularis mucosa*. In contrast to superficial gastrointestinal erosions peptic ulcers are characterized by the deeper defect (Fig. 1). Erosions never penetrate through the *muscularis mucosae*.

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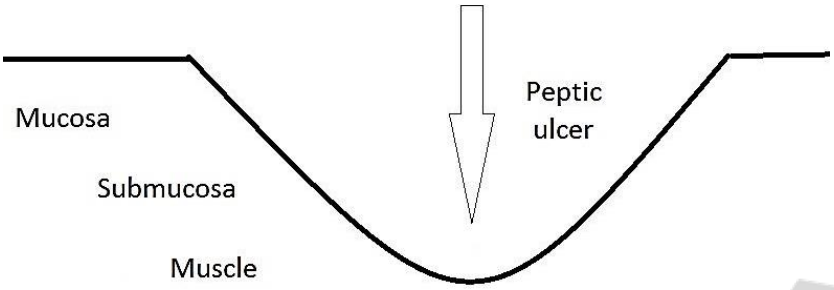

Fig. 1. Formation of peptic ulcer

Peptic ulcer disease is a chronic condition that affects stomach and/or duodenum (and sometimes esophagus) with recurring formation of peptic ulcers. This publication doesn't cover esophageal pathology.

The lifetime risk for peptic ulcer in individuals infected with *H. pylori* ranges from 3 % to 25 % worldwide. The annual incidence of the pathology is 0.10–0.19 % for physician-diagnosed cases and 0.03–0.17 % for cases diagnosed during hospitalization. Literature data show that the incidence of PUD has decreased over the last years in Western countries. It happened more likely due to successful eradication of *H. pylori*. The 3-year recurrence rate for PUD is less than 10 % in case of complete eradication of *H. pylori* in contrast with 50 % in patients with unsuccessful eradication.

The incidence of PUD rises with patient age and is similar is both genders.

ETIOLOGY AND PATHOGENESIS

Peptic ulcers occur when the lining of the stomach or duodenum becomes damaged, mainly by acid.

Normally, in 24 hours gastric parietal cells secrete about two liters of hydrochloric acid to aid digestion and to kill bacteria. Food protein in stomach stimulates gastrin output that triggers the release of histamine from enterochromaffin-like cells in the gastric body. In its turn, histamine stimulates H_2-receptors of parietal cells making them secrete acid. It is negative feedback control, that resulting pH fall causes liberation of somatostatin, which inhibits the production of gastrin.

In PUD, the misbalance of defense factors and factors of aggression leads to inflammation and formation of defects of lining. Weakened normal defense and repair mechanisms make the lining of stomach or duodenum more likely to be damaged by gastric acid.

In healthy individuals, gastrointestinal mucosa is protected by several factors:

– mucosal production of mucus (a barrier to the diffusion of acid and pepsin);

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– mucosal production of bicarbonate (creates neutral pH within and under the mucus);

– tight junctions of epithelial cells (prevent back diffusion of hydrogen ions);

– withdrawal of extra H^+ ions by membrane transport systems of epithelial cells;

– sufficient mucosal blood flow (removes hydrochloric acid that diffused through the epithelial layer);

– mucosal repair and maintenance of mucosal integrity by growth factors and prostaglandins.

Aggressive factors that break protective mechanisms of mucosa include:

– excessive acid secretion;

– high level of pepsin;

– *H. pylori* infection;

– NSAIDs;

– other drugs (glucocorticoids, bisphosphonates, etc).

The main etiological factors of ulcerogenesis in PUD are *H. pylori* infection and NSAIDs. About 95 % of duodenal ulcers and 70 % of gastric ulcers are caused by *H. pylori*. The percentage of gastric and duodenal ulcers associated with NSAIDs use is as high as 14–25 % worldwide.

H. pylori interferes in the normal balance between protective and aggressive factors via increasing acid production, damage of the stomach mucosa and producing toxins. It can be found in stool, saliva and teeth plaque and may be transmitted from person to person.

H. pylori produce urease, which degrades urea, thus releasing ammonia to protect it from gastric hydrochloric acid as well as to destroy and permeate the mucus layer. In addition, enzymes produced by the microorganism may contribute damage of mucosa and ulcer formation.

At the outset *H. pylori* leads to acute gastritis in the prepyloric zone, which later progresses to chronic gastritis. In case of gastric ulcer, despite the restriction of the secretory activity of the mucosa, secondary ulceration is possible due to the qualitative or quantitative deficiency of protective factors (mucus formation, epithelial consistency). Thus, decreased acid production gives rise to gastric ulcer disease. *H. pylori* can also cause hypergastrinemia, which results in enhanced secretion of hydrochloric acid and formation of duodenal ulcers.

NSAIDs contribute to mucosal inflammation and ulceration by inhibiting gastric prostaglandin production through suppression of COX-1 enzyme. NSAIDs that are selective COX-2 inhibitors have fewer adverse gastric effects. Farther, NSAIDs inhibit platelet activity and can increase the risk of bleeding from existing ulcers.

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A rare cause of PUD is Zollinger-Ellison syndrome with excess acid production.

Stress ulcers occur as a result of polytrauma, burns, major surgery and serious diseases such as kidney failure. Pathogenesis of Curling-type of stress ulcers in patients with severe burns is associated with weakening of the normal mucosal barrier due to decreased plasma volume and stomach blood flow with hypoxic tissue injury of gastric epithelium. Cushing-type of stress ulcers arises in patients with brain injury as a result of increased vagal stimulation which leads to an increased production of hydrochloric acid.

Such factors as cigarette smoking, family history of PUD can also increase the risk of ulceration.

CLASSIFICATION

Currently used classification of gastric and duodenal peptic ulcers takes into account:

1. Etiology
   - associated with *H. pylori* infection
   - not associated with *H. pylori* infection
2. Localization of ulcers:
   - gastric
   - duodenal
   - combined gastric and duodenal ulcers
3. Diameter of ulcers:

a) for gastric ulcers
   - small: less than 0.5 cm
   - medium-sized: 0.6–1.9 cm
   - large: 2.0–2.9 cm
   - giant: 3.0 cm and more

b) for duodenal ulcers
   - small: less than 0.5 cm
   - medium-sized: 0.6–0.9 cm
   - large: 1.0–1.9 cm
   - giant: 2.0 cm and more

4. Number of ulcers:
   - single
   - multiple
5. Disease activity

a) acute

b) chronic
   - with rare exacerbations (less than 1 time per year)
   - moderate (with exacerbations 1–2 times a year)

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– severe (with frequent exacerbations 3 times a year and more)

c) unspecified

6. Stage of ulcerative process:
   – active
   – scarring
   – red scar
   – white scar
   – long-term non-scarring
7. Complications
   – bleeding
   – penetration
   – perforation
   – perigastritis, periduodenitis
   – pyloroduodenal stenosis (compensated, subcompensated, decompensated)
   – malignization

Among the well-known classifications of PUD, special attention deserves to **modified Johnson classification** comprising:

Type I: Ulcer along the body of the stomach, most often along the lesser curve at *incisura angularis* along the *locus minoris resistantiae*.

Type II: Ulcer in the body in combination with duodenal ulcers. Associated with acid oversecretion.

Type III: In the pyloric channel within 3 cm of pylorus. Associated with acid oversecretion.

Type IV: Proximal gastroesophageal ulcer.

Type V: Can occur throughout the stomach. Associated with chronic NSAID use (such as aspirin).

Individual codes for peptic ulcers are assigned by **ICD-10** (Table 1). Marginal ulcers (late complication after gastric bypass surgery) at the gastrojejunal anastomosis are classified as gastrojejunal ulcers with code K28.

Table 1

ICD10 codes for gastric, duodenal, unspecified and gastrojejunal peptic ulcers

ICD10 code	Code description
K25	Gastric ulcer
K25.0	Gastric ulcer, acute with haemorrhage
K25.1	Gastric ulcer, acute with perforation
K25.2	Gastric ulcer, acute with both haemorrhage and perforation
K25.3	Gastric ulcer, acute without haemorrhage or perforation
K25.4	Gastric ulcer, chronic or unspecified with haemorrhage
K25.5	Gastric ulcer, chronic or unspecified with perforation
K25.6	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation

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ICD10 code	Code description
K25.7	Gastric ulcer, chronic without haemorrhage or perforation
K25.9	Gastric ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K26	Duodenal ulcer
K26.0	Duodenal ulcer, acute with haemorrhage
K26.1	Duodenal ulcer, acute with perforation
K26.2	Duodenal ulcer, acute with both haemorrhage and perforation
K26.3	Duodenal ulcer, acute without haemorrhage or perforation
K26.4	Duodenal ulcer, chronic or unspecified with haemorrhage
K26.5	Duodenal ulcer, chronic or unspecified with perforation
K26.6	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation
K26.7	Duodenal ulcer, chronic without haemorrhage or perforation
K26.9	Duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K27	Peptic ulcer, site unspecified
K27.0	Peptic ulcer, acute with haemorrhage
K27.1	Peptic ulcer, acute with perforation
K27.2	Peptic ulcer, acute with both haemorrhage and perforation
K27.3	Peptic ulcer, acute without haemorrhage or perforation
K27.4	Peptic ulcer, chronic or unspecified with haemorrhage
K27.5	Peptic ulcer, chronic or unspecified with perforation
K27.6	Peptic ulcer, chronic or unspecified with both haemorrhage and perforation
K27.7	Peptic ulcer, chronic without haemorrhage or perforation
K27.9	Peptic ulcer, unspecified as acute or chronic, without haemorrhage or perforation
K28	Gastrojejunal ulcer
K28.0	Gastrojejunal ulcer, acute with haemorrhage
K28.1	Gastrojejunal ulcer, acute with perforation
K28.2	Gastrojejunal ulcer, acute with both haemorrhage and perforation
K28.3	Gastrojejunal ulcer, acute without haemorrhage or perforation
K28.4	Gastrojejunal ulcer, chronic or unspecified with haemorrhage
K28.5	Gastrojejunal ulcer, chronic or unspecified with perforation
K28.6	Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation
K28.7	Gastrojejunal ulcer, chronic without haemorrhage or perforation
K28.9	Gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Only about 50 % of patients have typical symptoms of PUD. Clinical manifestations depend on ulcer localization, patient age and type of ulcer. Elderly patients often have a few or no symptoms of PUD. The symptoms of NSAID-associated ulcers, marginal ulcers and stress ulcers may not follow any pattern or can be asymptomatic.

The most common symptom of gastric ulcer is mild to moderately severe epigastric pain relieved by food or antacids. However, in some cases eating exacerbates rather than relieves pain. These patients may be afraid to eat and

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may lose weight. Burning, gnawing, aching, soreness or even a sensation of hunger can be the equivalents of the epigastric pain.

In patients with duodenal ulcers, pain in upper abdomen appears when the stomach is empty. It can awaken a patient at night and is relieved by eating or taking antacids. Consuming food reduces the pain temporarily, and in the fasting state it returns.

As mentioned earlier, PUD is dangerous for its complications. These include upper gastrointestinal bleeding, penetration and perforation of ulcers, development of perivisceritis, gastric outlet obstruction and malignant transformation.

Upper gastrointestinal **bleeding** of various severity is the most common complication of PUD. Bleeding can be the first presentation of peptic ulcers of stomach and duodenum. This complication can manifest as vomiting of bright red blood or partially digested blood ("coffee ground"), black tarry stools (melena), sweating, thirst, weakness, orthostatic hypotension and syncope.

Penetration of ulcer comes about from going of lesion through the muscular wall of the stomach or duodenum and continuing into an adjacent organ. The presentation of this complication is intense, persistent pain referred to sites other than abdomen (such as back pain) with severity dependent from body position.

Perforation is a very serious complication of PUD. It can manifest as a sudden, severe pain followed by rapid development of symptoms of acute abdomen. However, in elderly or very ill patients and those receiving corticosteroids or immunosuppressants clinical manifestations can be less severe.

Periviscerites that manifests in the form of perigastritis or periduodenitis, can start up in the acute phase of PUD when the inflammatory process goes to the surrounding organs and tissues. In patients with perivisceritis pain is associated with food intake, increases in the upright position and under lifting weights, and can still persist during the remission of PUD.

Pyloric stenosis can be a result of spasm, inflammation or scarring associated with ulcer. Gastric retention, bloating, nausea, large-volume vomiting especially at the end of the day suggest the diagnosis. Patients can also present weight loss associated with lack of appetite. Repeated vomiting can cause dehydration, electrolyte imbalance and alkalosis.

Risk of stomach **cancer** is increased in patients with *H. pylori*-associated PUD. Malignancies of duodenal ulcers are extremely rare. Signs of malignant transformation of ulcer are modification of pain characteristics (permanent, no connection with food intake), loss of appetite, meat aversion, weight loss, weakness, low-grade fever and symptoms of anemia.

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DIAGNOSIS

In classic cases of PUD palpation may reveal local tenderness in epigastrium. In stomach ulcers, pain is usually detected in the middle of epigastrium. In pyloric ulcers, pain can be localized to the right of the umbilicus and even in the right hypochondrium. Signs of PUD complications can also be identified by physical examination. In penetrating ulcers and ulcers complicated by adhesions, cutaneous hyperesthesia can be observed in the epigastric region, hypochondria and under the scapulae. In peritonitis abdominal palpation can reveal the evidences of acute abdomen.

Diagnosis of PUD is confirmed by upper gastrointestinal endoscopy or upper gastrointestinal series. Upper gastrointestinal endoscopy is crucial since it involves invasive methods for detection of *H. pylori* infection and biopsy for differential diagnosis with malignancy. Upon endoscopy peptic ulcer of stomach or duodenum is identified as a round or elongated defect of lining (Fig. 2).

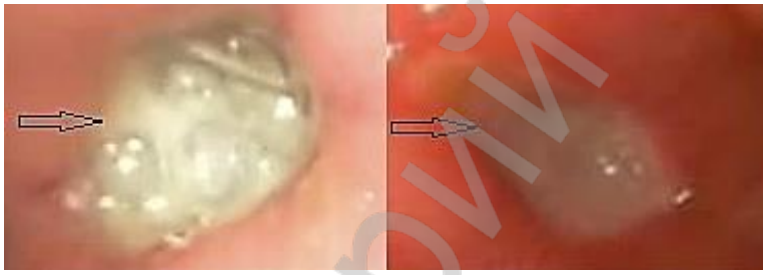

Fig. 2. Endoscopic images of peptic ulcers

Endoscopy is also helpful in diagnosis of such complication of PUD as bleeding. The abundant signs of peptic ulcer on upper gastrointestinal series are persistent depot of contrast barium suspension on the contour of organ and convergence of the folds of lining toward the ulcer (Fig. 3).

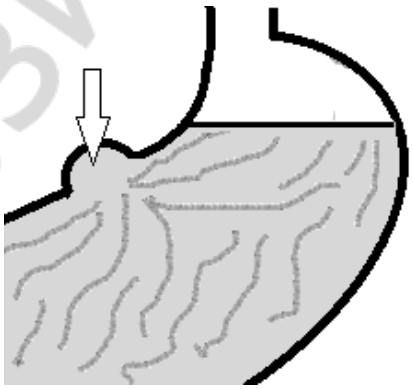

Fig. 3. Radiographic signs of peptic ulcer

Both upper gastrointestinal endoscopy and upper gastrointestinal series can be also helpful in detection of pyloric stenosis and penetration of ulcer.

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Abdominal X-ray, computed tomography and magnetic resonance imaging can be used as additional methods of diagnosis for pneumoperitoneum caused by perforated peptic ulcer.

Once the diagnosis of PUD has been made, tests for *H. pylori* infection are performed. This microorganism can be detected by invasive and noninvasive methods (Table 2). As some medications can decrease their sensitivity, it is essential that a patient should keep clear of antibiotics and bismuth salts within 4 weeks, and PPIs should be discontinued at least 2 weeks before testing.

Table 2

Tests for detection of *H. pylori*

Noninvasive tests	Invasive tests
Urea breath test: – requires the ingestion of urea labeled with the nonradioactive isotope ^{13}C- or ^{14}C-; the urea is hydrolyzed by bacterial urease to labeled CO_2, which is measured in the expired air	Rapid urease test: – most commonly used (from invasive tests); – bacterial urease degrades urea to ammonia in a mucosa specimen that causes color change on a special medium
H. pylori stool antigen test: – identifies current infection by detecting antigens that are produced by live *H. pylori* bacteria and dropped into the stool	Histology of a mucosal specimen: – the density of *H. pylori* can vary at different sites, this can lead to false result
Serologic assays for antibodies to *H. pylori:* – reveal evidence of an active or previous *H. pylori* infection; – are not used for cure assessment	Bacterial culture of a mucosal specimen: – allows to determine antimicrobial sensitivity in refractory *H. pylori* infection

Invasive tests following upper gastrointestinal endoscopy require mucosal biopsy, and thus, they are not applicable in patients who don't need endoscopy for other reasons. Urea breath test and *H. pylori* stool antigen test are preferred for initial diagnosis and posttreatment control to confirm eradication of the microorganism.

In patients suspicious for Zollinger-Ellison syndrome (multiple ulcers, atypical locations of ulcers, refractoriness to treatment, diarrhea and weight loss) serum gastrin levels should be measured to confirm the diagnosis.

For patients with peptic ulcers resistant to standard antisecretory therapy 24-hour gastric pH monitoring should be assigned.

DIFFERENTIAL DIAGNOSIS

The symptoms of PUD can be nonspecific. Conditions that may appear with epigastric pain or discomfort include functional dyspepsia, gastroesophageal reflux disease, gastric cancer, gallstone attack and pancreatitis (Table 3).

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Table 3

Differential diagnosis of peptic ulcer disease

Disease	Differentiating signs	Differentiating tests
Functional dyspepsia	dyspepsia lasts for at least three months without any organic or metabolic cause	a diagnosis of exclusion with no relevant abnormality in laboratory and instrumental testing
Gastroesophageal reflux disease	heartburn and regurgitation, sometimes laryngitis and cough	upper gastrointestinal endoscopy detects no stomach or duodenal ulcers and, often, esophagitis or erosions in esophagus
Gastric cancer	alarm signs such as weight loss, anorexia, bleeding, anemia, early satiety and dysphagia; a palpable mass	upper gastrointestinal endoscopy with biopsy verifies malignancy
Gallstone attack	sharp right upper quadrant pain that can radiate to the right shoulder	abdominal ultrasound and computed topography suggest gallstones, cholecystitis or choledocholithiasis
Acute pancreatitis or exacerbation of chronic pancreatitis	severe abdominal pain in the upper abdomen which typically radiates to back	high levels of serum amylase and lipase; abdominal ultrasound and computed tomography detect inflammation of pancreas

TREATMENT

Treatment of PUD includes life-style modification, diet changes and drugs. Urgent requirement of surgery can be explained by onset of complications such as perforation, pyloric stenosis, bleeding, perforation and malignization. In very rare cases, surgery may be performed to treat PUD that do not respond to drug therapy. However, surgical treatment does not preclude any chance of ulcer recurrence. A crucial point in treatment of PUD is that number of patients requiring surgery decreased significantly due to the current drug therapy.

Lifestyle modifications for treatment of PUD implicate avoidance of such risk factors as NSAIDs use and smoking. By now, there are no arguments to prove rigorously that any specific diet intensifies healing of ulcers and helps to prevent recurrence. Thus, it is recommended to avoid foods that worsen symptoms. For the period of PUD recurrence alcohol consumption should be stopped.

Drug therapy of PUD is based on use of acid-suppressive drugs and eradication of *H. pylori* (if identified).

SUPPRESSION OF GASTRIC ACIDITY

For reduction of gastric acidity PPIs are used in most of the cases. Now they play an increasingly important role in clinical practice and replace

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H_2-blockers. Their mechanism of action is associated with irreversible inhibition of H^+-K^+-ATPase (the proton pump), leading to rejection of proton translocation across the plasma membrane of gastric parietal cells, resulting in nearly 90 % reduction of acid secretion by these cells. Owing to the impact on the terminal phase of stomach acid production, PPIs are the most effective means of reducing gastric acidity.

PPIs are usually well tolerated. The most common side effects are nausea, constipation, headache, fatigue and dizziness. PPIs can interact with other drugs. Omeprazole decreases deactivation of clopidogrel reducing its antiplatelet effect. Lansoprazole, omeprazole, rabeprazole and esomeprazole can prolong the elimination of warfarin and cause abnormal bleeding. Standard doses of PPIs (Table 4) are taken once daily, in the morning, 20–30 minutes before a meal. With severe clinical manifestations, double doses of PPIs are allowed.

Table 4

Standard doses of proton pump inhibitors

PPIs	Standard doses, mg
Omeprazole	20
Lansoprazole	30
Pantoprazole	40
Rabeprazole	20
Esomeprazole	20 (40)

In bleeding ulcers PPIs can be used intravenously as a component of complex therapy.

In patients who do not tolerate PPIs, H_2-blockers still can be used. Since 1970s until the early 1990s, they were the most commonly prescribed drugs in the world. After introduction of PPIs, the use of H_2-blockers significantly dropped. These medications inhibit the secretion of hydrochloric acid stimulated by histamine by reversible competing with this organic compound for binding to H_2-receptors on the basolateral membrane of parietal cells.

H_2-blockers suppress acid secretion by up to 70 % over a 24-hour period, hence they are less effective than PPIs. For another thing, their repeated dosing leads to tolerance. Dosage of famotidine is 40 mg once a day at bedtime; ranitidine is taken 150 mg BID or 300 mg once a day at bedtime. Their most common side effects are headache, dizziness, diarrhea and constipation.

Duration of antisecretory therapy is 4–6 weeks for duodenal ulcer and 8–10 weeks for stomach ulcer, or until the ulcer heals. If eradication therapy is needed, use of acid-suppressive drugs should be continued after completing of it up to reaching this duration or the ulcer healing.

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ANTACIDS AND MUCOSAL PROTECTIVE AGENTS

Antacids neutralize stomach acid and thereby relieve symptoms of PUD. These drugs can be used in the early stage of antisecretory treatment. Effectiveness depends on the amount of antacid taken and the level of gastric acidity. They can interfere with absorption of many other medications. Commonly used aluminum hydroxide can cause weakness, loss of appetite and constipation. Magnesium hydroxide is a more effective than aluminum hydroxide, but in high doses it can induce diarrhea. Antacids can contain both magnesium hydroxide and aluminum hydroxide to limit diarrhea.

Group of mucosal protective agents include sucralfate and bismuth compounds. They increase the resistance of the stomach and duodenum mucosa to the aggressive action of gastric juice.

In acidic solutions, sucralfate forms a viscous polymer that binds selectively to ulcers or erosions for up to 6 hours. It can be a reasonable alternative to antacids. Sucralfate is activated by acid, therefore concurrent use of antacids should be avoided. The most common side effect of sucralfate is constipation.

Bismuth creates a protective layer coating ulcers and erosions. In addition, bismuth compounds possess direct antimicrobial activity against *H. pylori*. Bismuth agents can cause constipation and harmless darkening of the stool, which can be mistakenly estimated as a sign of gastrointestinal bleeding.

ERADICATION OF *H. PYLORI*

Over the years since the discovery of *H. pylori*, various regimens of elimination of the microorganism with antibiotics have been proposed. High resistance of *H. pylori* to antibiotics contributed to development of special eradication therapy methods. Currently, only the treatment methods included in Maastricht V/Florence Consensus are of practical importance.

The most frequently used anti-*Helicobacter* scheme is **triple therapy** (first-line therapy) with standard or sequential regimen (Table 5).

Table 5

Regimens of triple therapy for eradication of *H. pylori*

Standard regimen	Sequential regimen
PPI in a standard dose BID + clarithromycin 500 mg BID + amoxicillin 1000 mg BID (or metronidazole 500 mg BID in amoxicillin resistant strains) for 10–14 days	PPI in a standard dose BID + amoxicillin 1000 mg BID for 5–7 days; then PPI in a standard dose BID + clarithromycin 500 mg BID + metronidazole/tinidazole 500 mg BID for 5–7 days

Second- and third-line treatment options for *H. pylori* infection are bismuth-containing quadruple therapy and triple therapy with levofloxacin, respectively.

Bismuth-containing quadruple therapy is prescribed for 10-14 days and comprises:

– PPI in the standard dose BID;
– colloidal bismuth subcitrate 120 mg QID;
– tetracycline 500 mg QID;
– metronidazole (tinidazole) 500 mg TID.

The following drugs are given for 10–14 days as **triple therapy with levofloxacin**: PPI in a standard dose BID in combination with levofloxacin 500 mg BID and amoxicillin 1000 mg BID.

It is not easy to eliminate *H. pylori* in some patients. Ineffectiveness of the therapy can be determined by such factors as:

– inappropriate eradication regimen;
– low compliance;
– high microbial loads;
– invasion of gastric epithelium cells by *H. pylori;*
– high acidity of gastric juice;
– CYP2C19 genetic polymorphism;
– formation of microbial biofilm (tolerance to antibacterial drugs and host immune defense factors);
– antibiotic resistance.

However, some of the listed factors causing treatment failure can be resolved.

Following the prescribed therapy is one of the most important factors for the successful eradication of *H. pylori*. Low compliance can cause microbial resistance to antibiotics, development of serious complications and lowering the quality of life. A doctor has to motivate a patient by providing him information about *Helicobacter*-associated diseases and risk of serious complications.

Definitely, it is easier to achieve high compliance with a shorter duration of treatment and fewer well tolerated drugs. However, time makes reasonable adjustments. *H. pylori* resistance to antibiotics is increasing in most countries of the world. Unsuccessful results of standard triple therapy are determined in most of the cases by resistance of the bacterium to clarithromycin.

In accordance with Maastricht V/Florence Consensus, if the level of *H. pylori* resistance to clarithromycin in the region is above 15 %, the PPI-clarithromycin containing triple eradication regimen can be used only after assessing the microorganism's sensitivity to this antibiotic. Patient interview also plays an important role because pharmaceutical anamnesis allows to suspect the high drug resistance in a patient despite the low resistance in the population.

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With high tolerance to clarithromycin in the region (> 15 %), the choice of the optimal treatment regimen should be based on the findings on resistance to metronidazole and double resistance to clarithromycin and metronidazole.

Currently, no bismuth-resistant *H. pylori* strains has been reported. In areas of high (> 15 %) clarithromycin resistance, bismuth quadruple (PPI + colloidal bismuth subcitrate + tetracycline + metronidazole) or non-bismuth quadruple, concomitant (PPI + amoxicillin + clarithromycin + nitroimidazole) therapies are recommended.

In case of high dual resistance to clarithromycin and metronidazole, bismuth-based quadruple regimen is recommended as a first-line therapy. In addition, bismuth-based quadruple therapy can be preferred if the patient is allergic to penicillin and resistance to clarithromycin in the population is high.

In absence of effect of quadruple therapy based on bismuth preparations, a levofloxacin-based eradication regimen can be used.

PPIs play an important role in *H. pylori* eradication because they increase pH of the stomach. At pH above 6, *H. pylori* transforms in the vegetative replicative state in which it is most sensitive to amoxicillin and clarithromycin. At the same pH values, the half-lives of these antibiotics are maximal.

Metabolism and subsequent pharmacological efficacy of PPIs largely depend on the activity of liver cytochrome P450 enzymes. Genetic polymorphism of CYP2C19 isoenzyme, which is involved in the metabolism of PPIs, predetermines inter-ethnic differences in drug response. There are several patient phenotypes: fast metabolizers, intermediate metabolizers and slow metabolizers. Levels of PPIs in plasma and stomach pH are lowest in the group of rapid metabolizers. The fast metabolizing phenotype is most common in Europe and North America. Use of high-doses of PPIs BID increases the effectiveness of triple therapy in such patients.

Maastricht V/Florence Consensus indicates the need to increase a duration of eradication therapy to 14 days, if at the regional level the treatment with a duration of 10 days has not shown the effectiveness. Prolongation of eradication regimen helps to overcome the resistance to metronidazole.

Use of probiotics as an adjuvant therapy increases the effectiveness of eradication. Probably, this result is achieved due to keeping of normal intestinal microbiota, inhibition of *H. pylori* or competition with this bacterium for colonization and survival, maintenance of the barrier function of gastrointestinal mucosa, prevention of colonization by pathogenic microorganisms and participation in modulation of local and systemic immune response. Positive influence on eradication can be associated with reduction of the side effects of antibiotics (diarrhea, nausea, vomiting, flatulence and abdominal pain).

Thus, methods that help to optimize anti-*Helicobacter* treatment include increase of patient compliance, consequent use of various eradication regimens and their prolongation, taking the regional sensitivity of the microorganism to

antibacterial drugs into consideration, prescribing of double doses of PPIs, and introducing of probiotics as an adjuvant therapy.

CONTROL OF PEPTIC ULCER HEALING AND CONFIRMATION OF *H. PYLORI* ERADICATION

Healing of a stomach ulcer is controlled endoscopically within 2–8 weeks from the start of antisecretory treatment until the ulcer heals completely. To exclude malignancy biopsy is taken from the post-ulcer scar or from the base and margins of unhealed ulcer. Healing of duodenal ulcers is controlled by upper endoscopy within 2–6 weeks from the beginning of acid-suppressive treatment. No endoscopic control is allowed in uncomplicated duodenal ulcers with completing of eradication therapy and discontinuation of clinical manifestations.

Confirmation of eradication should be done at least 1 month after the finishing of anti-*Helicobacter* therapy (see section Diagnosis).

PREVENTION AND PROGNOSIS

About 95 % of duodenal ulcers heal within 4 weeks, and 80–90 % of stomach ulcers heal in 8 weeks. According to literature, the 3-year recurrence rate for PUD is less than 10 % in case of successful eradication of *H. pylori* versus more than 50 % for failure of eradication. Besides *H. pylori* infection, among the factors influencing the recurrence of PUD are long-term NSAIDs use and smoking. If the impact of these factors is cancelled, the prognosis for the patient is favorable.

Good hygiene diminishes the risk of *H. pylori* infection and exacerbation of PUD. To reduce the spread of the microorganism patients should wash hands thoroughly with soap and avoid sharing tableware and cutlery.

Secondary prevention of PUD with acid-suppressive medications comprises:

– continuous maintenance therapy;

– intermittent therapy, which requires intermittent episodes of continuous therapy for 3–6 months followed by discontinuation;

– on-demand therapy.

Indications for the above-mentioned types of preventive use of antisecretory medications are presented in Table 6.

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Table 6

Indications for preventive use of acid-suppressive medications

Type of therapy	Indications
Continuous maintenance therapy	Zollinger–Ellison syndrome; regular use of NSAIDs and history of PUD; refusing by patient to undergo surgery in complicated PUD
Intermittent therapy	severe disease; concomitant gastroesophageal reflux disease and esophagitis; history of complications of PUD
On-demand therapy	rare exacerbations of PUD; moderate PUD with no risk factors for recurrence

CASE STUDY

A 46-year old man presents to a primary care physician with complains on weakness, tiredness, dizziness, headache and one-month intermittent upper abdominal pain. The pain is dull and gnawing. It sometimes wakes the patient at night and can be relieved by food. The patient has a history of smoking for 20 years. About two months ago he started taking diclofenac to control the lower back pain. About a week ago the patient noted the appearance of a dark tarry stool.

Physical examination reveals such abnormal findings as paleness of the conjunctiva and skin, systolic murmur best heard at the heart's base, tachycardia (heart rate is 115 per minute), arterial hypotension (blood pressure is 105/60 mm Hg), and mild epigastric tenderness on palpation of the upper abdomen.

Questions:

1. What suppositional forms of pathology did the patient develop?
2. Which of them is primary?
3. Specify additional tests to confirm the diagnosis. Outline their probable findings.
4. Prescribe treatment.

Answers:

1. Duodenal peptic ulcer, bleeding, posthemorrhagic iron-deficiency anemia.
2. Bleeding is a complication of duodenal ulcer. Iron deficiency anemia occurred as a result of bleeding.
3. General blood test (decreased levels of red blood cells and hemoglobin), blood biochemistry (low serum iron; serum ferritin can be also decreased), fecal occult blood test (presence of blood), upper gastrointestinal endoscopy (presence of duodenal peptic ulcer, signs of existing or completed bleeding).
4. Treatment is based on consulting with surgeon (to define the necessity of surgery), PPIs, iron supplements.

РЕПОЗИТОРИЙ БГМУ

SELF-CONTROL TEST

1. Peptic ulcer disease comprises:
a) diabetic foot ulcer;
b) damage to the lining of the stomach;
c) damage to the lining of the duodenum;
d) pressure ulcers.

2. A peptic ulcer is a lesion in a segment of the gastrointestinal mucosa that penetrates through the *muscularis mucosae:*
a) true;
b) false.

3. Etiology of peptic ulcer disease:
a) *H. pylori* infection;
b) disturbances in colonic motility;
c) NSAIDs;
d) increased sensitivity to food or gas.

4. Pain in duodenal ulcers:
a) is associated with bloating;
b) is exacerbated by eating;
c) awakens a patient at night;
d) is relieved by food but recurs 2 to 3 h after a meal.

5. Diagnosis of peptic ulcer disease is based on:
a) upper gastrointestinal series;
b) upper gastrointestinal endoscopy;
c) lower gastrointestinal endoscopy;
d) blood biochemistry.

6. Proton pump inhibitors should be discontinued at least _____ before the tests for *H. pylori*:
a) a month;
b) 2 weeks;
c) 1 week;
d) 10 days.

7. Noninvasive tests for *H. pylori* include:
a) urea breath test;
b) histology;
c) bacterial culture;
d) stool antigen test.

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8. Treatment of peptic ulcer disease includes:

a) antibiotics;
b) acid-reducing drugs;
c) antacids;
d) NSAIDs.

9. Second-line empiric regimen in case of failure of standard triple therapy (clarithromycin based) for eradication of *H. pylori*:

a) PPI + colloidal bismuth subcitrate + clarithromycin;
b) PPI + colloidal bismuth subcitrate + amoxicillin;
c) PPI + doxycycline + amoxicillin;
d) PPI + colloidal bismuth subcitrate + tetracycline + metronidazole.

10. Complications of peptic ulcer disease:

a) abscesses;
b) pyloric stenosis;
c) small intestinal bacterial overgrowth;
d) upper gastrointestinal bleeding.

Correct answers: 1 – b, c; **2** – a; **3** – a, c; **4** – c, d, **5** – a, b; **6** – b; **7** – a, d; **8** – a, b, c; **9** – d; **10** – b, d.

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