Ministry of Healthcare of Ukraine

Poltava State Medical University

Approved
at the meeting of Internal Medicine №1
Department "____"_____
Protocol № ____ from _____
The Head of the Department
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Methodical guidelines

for students' self-studying to prepare

for practical (seminar) classes and on the lessons

Academic discipline	Internal medicine
Module №	1
Topic of the lesson	Gastroesophageal reflux disease. Dyspepsia.
Course	IV
Faculty	of foreign students training

1. Relevance of the topic: Gastroesophageal reflux disease (GERD or GORD) is common medical disorder of young and elder patients and frequently associates with other gastrointestinal (GI) pathology.

Dyspepsia can be considered as complex of symptoms typical for the wide range of GI diseases, as well as separate nosology called "functional dyspepsia" (FD), management of which is regulated by Rome IV criteria.

2. Certain aims:

– To analyze symptoms from upper GI tract and make the preliminary diagnosis.

– To explain pathogenesis of GERD and functional dyspepsia generally and in individual patients.

– To propose further management tactics for those with suspected GERD or FD.

– To classify GERD and FD.

– To interpret data of CBC, EGDS, 24-hours pH-monitoring and HP tests.

– To draw schemes, charts of patient's follow-up.

– To analyze data of survey, physical examination, additional methods of investigations to confirm the clinical diagnosis of patients with suspected GERD and FD.

– To make the full diagnosis according to the current classifications and prescribe treatment for patients with GERD and FD.

3. Basic knowledge, abilities, skills required to study the topic (interdisciplinary integration).

Names of previous disciplines	Obtained skills
1. Anatomy 2. Histology 3. Anatomy 4. Physiology 5. Pathology	To describe the structure of the gastrointestinal tract, blood supply and innervation in health and disease; to establish the preliminary diagnosis, to use additional methods of examination

6. Radiology 7. Propaedeutic internal medicine 8. Pharmacology	and interpret their data to make final diagnosis; to manage the patient with GERD and FD; to classify GERD, FD, and drugs for their treatment; to identify markers of gastrointestinal tract function and to know their normal values; to draw a scheme of patient's follow-up; to compare GERD and FD with other diseases with the same symptoms; to demonstrate practical skills during physical examination of the patient, analyzing the clinical and laboratory results.

4. Tasks for self-studying to prepare for the lesson and on the lesson.

4.1. List of main terms, parameters, characteristics that should be learnt by student during preparation for the classes:

Term	Definition
GERD	is a chronic recurring disease which results from the retrograde flow of gastric contents back into the esophagus (gastro-esophageal reflux), oropharynx, and/or respiratory tract and causes troublesome symptoms and/or mucosal injury.
Dyspepsia	1) complex of symptoms including: pain or discomfort in epigastrium, heaviness or postprandial fullness,

	bloating, heartburn, nausea, regurgitation and belching; 2) disease, known as “functional dyspepsia” which is characterized by one or more of the following symptoms: epigastric pain, epigastric burning, postprandial fullness, and early satiation that are unexplained after a routine clinical evaluation.
Antacids	group of drugs that reduce stomach acidity and capable to neutralise the effects of stomach acid (PPIs and H2-blockers).
Alginates	group of drugs capable to neutralise the effects of stomach acid by coating formation on the surface of stomach.

4.2. Theoretical questions for the lessons:

1. What is GERD and FD?
2. How GERD and FD should be classified?
3. What are the risk factors for GERD and FD?
4. Explain the pathophysiological mechanisms of GERD and FD.
5. Name the diagnostic criteria of GERD and FD.
6. What are the endoscopic characteristics of GERD and its stages?
7. Specify the principles and features of GERD and FD pharmacotherapy according to modern recommendations.
8. What lifestyle modifications should be recommended for patients with GERD and FD?
9. What are the approaches to GERD and FD prevention?

4.3. Practical work (tasks), performed on the lesson:

1. Interpret changes in general blood test in case of GERD or FD.
2. Interpret data of biochemical blood tests in case of GERD or FD.
3. Interpret data of EGDS, 24-ph monitoring, HP tests in case of GERD or FD.
4. Perform survey and physical examination of the patient and make preliminary diagnosis.
5. Manage the patient with suspected GERD or FD, prescribe relevant laboratory and instrumental investigations and further treatment.

Topic content:

GASTRO-ESOPHAGEAL REFLUX DISEASE

Gastro-esophageal reflux disease (GERD) – chronic disease that results from the backflow of gastric contents into the esophagus (gastro-esophageal reflux), causing specific symptoms and/or mucosal damage. Pay attention that there is a difference between GERD and physiologic reflux.

Montreal Classification of GERD (2006): erosive GERD (with esophagitis), nonerosive GERD (is characterized by the absence of mucosal breaks on endoscopy), Barret's esophagus (with long segment or short segment). Notice that erythema is not reliable finding for diagnosis of reflux esophagitis!

LA Classification of Esophagitis by grade (1999):

Grade A – one (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds;

Grade B – one (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds;

Grade C – one (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involve less than 75% of the circumference;

Grade D – one (or more) mucosal break which involves at least 75% of the esophageal circumference

GERD may be subclassified by symptoms: typical and atypical form.

GERD, defined as at least weekly heartburn or acid regurgitation, has a prevalence ranging from 10 to 20% in the Western world and less than 5% in Asia. The prevalence of heartburn is the highest in USA and Western Europe countries (20%) and the lowest is in China (2,5%).

Risk and etiological factors: obesity, pregnancy, hiatal hernia, tobacco abuse, alcohol consumption, overeating, taking medicines that decrease lower esophageal sphincter contractility (nitrates, calcium channel blockers, beta adrenergic agonists, papaverine, no-spa, anticholinergics, theophylline, morphine, meperidine, diazepam, and barbiturates etc.). A genetic component may also play a role in GERD exacerbation. Character of food can have an influence too, e.g. peppermint, coffee, fatty meal etc.

Pathogenesis. The esophagus is protected from the harmful effects of refluxed gastric contents by the antireflux barrier at the gastroesophageal junction, by esophageal clearance mechanisms, and by epithelial defensive factors. The antireflux barrier consists of the lower esophageal sphincter, crural diaphragm, phrenoesophageal ligament, and the angle of His, which causes an oblique entrance of the esophagus into the stomach. The attachment of the lower esophageal sphincter to the crural diaphragm results in increased pressure during inspiration and when intra-abdominal pressure increases. Disruption of normal defense mechanisms leads to pathologic amounts of reflux. Reflux of gastric contents from the stomach into the esophagus occurs in healthy individuals, but refluxed gastric contents are normally cleared in a two-step process: volume clearance by peristaltic function and neutralization of small amounts of residual acid by weakly alkaline swallowed saliva. In normal healthy individuals, physiologic reflux occurs primarily when the lower esophageal sphincter transiently relaxes in the absence of a swallow because of a vagally mediated reflex that is stimulated by gastric distention. Physiologic reflux is postprandial, shot, asymptomatic and does not cause mucosal injuries of esophagus.

In GERD patients, transient relaxation of the lower esophageal sphincter or a low resting lower esophageal sphincter pressure can result in regurgitation,

especially when intra-abdominal pressure is increased. Obesity results in an increase in intragastric pressure, which increases the gastroesophageal pressure gradient and the frequency of transient lower esophageal sphincter relaxation, thereby predisposing gastric contents to migrate into the esophagus.

Clinical features: The classic symptoms of GERD are:

– heartburn;

– acid regurgitation.

Typical symptoms of GERD:

1) Heartburn

– Retrosternal burning sensation

– Most commonly post-prandial, nocturnal

– Fatty foods, spicy foods, acidic foods

– Relived with antacids, water, milk

– Worsened with recumbency

2) Acid Regurgitation

– Perception of gastric content reflux in the mouth or hypopharynx

– Taste: bitter, acidic

Atypical symptoms:

1) Atypical

– Dysphagia, odynophagia

– Nausea

– Chest pain

– Dyspepsia (non-severe upper abdominal discomfort)

– Epigastric fullness, bloating

– Frequent belching

– Heartburn

2) Extraesophageal

– Chronic cough, bronchospasm, pneumonia, fibrosis

– Cardial pain, arrhythmia

– Hoarseness, laryngitis, pharyngitis, globus sensation, vocal cord dysfunction

– Stomatitis, dental erosions

Alarm (“RED FLAGS”) symptoms:

- Dysphagia (immediately assess for Barrett's Esophagus)
- Odynophagia (Assess for Esophageal Ulcer)
- Nausea/vomiting
- Melena
- Weight loss, anorexia
- Extended duration of symptoms with no response to PPIs
- Family history of peptic ulcer disease
- Symptom onset in the age more than 45 years, especially in males (high risk)
- High body temperature
- CBC changes (anemia, leukocytosis, etc.)

Diagnosis should be based on:

- History (patients’ complaints, anamnesis)
- Physical examination
- Screening tests (CBC)
- Empiric trial (IPP, Alginates)
- Additional tests: endoscopy with biopsy, chromoendoscopy, manometry, pH testing, impedance.
- If necessary: bronchography, ultrasound diagnostic, Helicobacter pillory testing, ECG.

When GERD presents with typical signs and symptoms, such as heartburn or acid regurgitation, that are responsive to antisecretory therapy, no diagnostic evaluation is warranted.

Diagnostic endoscopy is warranted in individuals who fail to respond to therapy or have alarm symptoms (“red flags”). Endoscopy permits the detection of erosive esophagitis and complications such as a peptic stricture and Barrett’s esophagus; mucosal biopsy, which is crucial in these settings, also excludes conditions that can mimic GERD, such as eosinophilic esophagitis.

Esophageal manometry is useful to exclude achalasia in patients with suggestive symptoms. Esophageal reflux testing by 24-hour transnasal pH monitoring, by 48-hour devices attached to the esophageal lumen, or by 24-hour combined impedance and pH monitoring, may be performed while patients are not on therapy to detect pathologic acid and nonacid reflux as well to correlate reflux events with atypical symptoms, especially in patients with normal endoscopies.

Barium radiography has no role in the diagnostic evaluation of patients with reflux disease.

Complications: esophageal strictures, Barrett's esophagus, ulcer of esophagus, bleeding, laryngitis, pharyngitis, sinusitis, adenocarcinoma, interstitial fibrosis, dental erosions (dental enamel loss).

Alternative diagnosis in GERD (Differential Diagnosis):

Coronary artery disease (ischemic heart disease), gallstones, gastric/esophageal cancer, peptic ulcer disease, esophageal motility disorders, pill induced esophagitis, eosinophilic esophagitis, fungal or viral esophagitis, peptic stricture, metaplastic disease (Barrett's), dysplastic disease (adenocarcinoma)

Treatment. General Measures:

– Avoidance of foods or beverages that may provoke symptoms, such as alcohol, coffee, spicy foods, fatty food, chocolate etc. and late meals (less than 2-3 hours before bedtime)

– Elevation of the head of the bed to 30 degrees for patients with nocturnal regurgitation or heartburn

– Weight loss for obese patients

– Tobacco cessation.

Medications. Inhibition of gastric acid secretion is the cornerstone of the acute treatment of GERD, and proton pump inhibitors (PPIs) are superior to histamine (H2)-receptor antagonists for both the healing of esophagitis and the control of symptoms. Once-daily standart dosage of PPIs 30-60 minutes prior to meal for 4-8 weeks (nonerosive form, Grade A, B) or 8-12 weeks (Grade C, D) is adequate. High dose (twice daily) is usually used for severe or refractory symptoms.

H2-receptor antagonists are useful in patients who are intolerant of PPIs, and can be used at bedtime to supplement PPIs in patients who have persistent symptoms.

PPIs (standart dosage):

- Esomeprazole 40mg
- Lansoprazole 30mg
- Omeprazole 20mg
- Pantoprazole 40mg
- Rabeprazole 20mg
- Dexlansoprazole (long-acting form) 60mg

H2-blockers interfere with acid production by blocking or antagonizing the actions of histamine. Histamine encourages acid secretion in the stomach. Famotidine is the most potent H2 blocker.

Also antacid medications (e.g. Maalox) can be used. Antacids neutralize acids in the stomach, and are the drugs of choice for mild GERD symptoms. They may also stimulate the defensive systems in the stomach by increasing bicarbonate and mucus secretion. They should be prescribed 1-1,5 hours after meal.

Magnesium salts have major side effect of diarrhea. Magnesium salts offered in combination products with aluminum (Maalox) to balance the side effects of diarrhea and constipation.

Prokinetic drugs help the stomach empty its contents more quickly and strengthen the esophageal sphincter. These are considered second-line access drugs due to side effects. The most widespread prokinetics are: Domperidone 10mg 3 times a day, Itoprid 50mg 3 times a day.

FUNCTIONAL DYSPEPSIA

Definition. Functional dyspepsia (FD) is a medical condition that is characterized by one or more of the following symptoms: epigastric pain, epigastric burning, postprandial fullness, and early satiation that are unexplained after a routine clinical evaluation. Abdominal bloating and nausea also may be experienced, but

they are less specific and are not considered cardinal symptoms of functional dyspepsia. Patients, who were not observed can be made a preliminary diagnosis of “uninvestigated dyspepsia”.

Classification. In the Rome IV criteria (2016), symptoms have been divided into postprandial distress syndrome and epigastric pain syndrome.

Pathogenesis. The pathobiology of functional dyspepsia is complex and multifactorial and not fully understood.

Gastroduodenal motor and sensory dysfunction, as well as impaired mucosal integrity, low-grade immune activation, and dysregulation of the gut-brain axis have all been implicated. So the factors, that play a role in FD pathogenesis are:

- delayed gastric emptying
- impaired gastric accommodation
- gastric and duodenal hypersensitivity to distention, acid, and other intraluminal stimuli
- Helicobacter pylori infection
- psychosocial factors.

Diagnosis. Dyspepsia can be suspected to be functional based on a clinical history consistent and the absence of alarm features, treatment of overlapping gastroesophageal reflux disease and H. pylori. The presence of anxiety, in particular symptom-related anxiety and comorbid IBS, increases the likelihood of functional dyspepsia.

The physical examination is generally normal, although epigastric tenderness may be present.

Aditional methods of laboratory and instrumental examination, besides upper endoscopy and HP testing, are: CBC, biochemical blood analysis, fecal occult blood test, ultrasound diagnostic of abdominal cavity, computer tomography.

Rome IV (2016) diagnostic criteria for functional dyspepsia (criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis):

1. One or more of the following:

Bothersome postprandial fullness/early satiation/epigastric pain/epigastric burning

2. No evidence of structural disease

(including at upper endoscopy) that is likely to explain the symptoms.

Rome IV (2016) diagnostic criteria for subgroups of patients with functional dyspepsia:

– Postprandial Distress Syndrome

Must include one or both of the following at least 3 days per week:

1. Bothersome postprandial fullness (severe enough to impact on usual activities)

2. Bothersome early satiation (severe enough not to finish a regular-size meal)

AND No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

– Epigastric Pain Syndrome

Must include one or both of the following at least 1 day per week:

1. Bothersome epigastric pain (severe enough to impact on usual activities)

2. Bothersome epigastric burning (severe enough to impact on usual activities) AND No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

Differential Diagnosis. Common organic causes of dyspepsia include peptic ulcer disease and gastroesophageal reflux disease. Delayed gastric emptying is present in a small number of patients with functional dyspepsia but is characteristic and more pronounced in patients with diabetic or idiopathic gastroparesis. Vomiting of undigested food is characteristic of these forms of gastroparesis, but not of dyspepsia. Gastric and esophageal cancers may also present with symptoms of dyspepsia but are much less common. Pancreaticobiliary disorders (including sphincter of Oddi dysfunction, chronic pancreatitis, or pancreatic cancer) also occasionally mimic dyspepsia.

Treatment. Reassurance, education, lifestyle, and dietary recommendations (more frequent, smaller meals and avoiding meals with high fat content) are frequently recommended to FD patients. Avoidance of nonsteroidal anti-inflammatory drugs, coffee, alcohol, and smoking is commonly recommended.

Eradication of H. pylori is recommended in patients with chronic dyspepsia and positive HP tests (according to Maastricht IV).

Postprandial distress syndrome should be treated with prokinetics (cisapride and domperidone). Itopride is a novel prokinetic agent that works by antagonizing dopamine D2-receptors and inhibiting acetylcholinesterase, and has been shown to improve postprandial fullness and early satiety with a low rate of adverse reactions. Acotiamide is a novel compound with fundusrelaxing and gastroprokinetic properties, based on a procholinergic effect that improves dyspepstic symptoms over placebo.

In relieving epigastric pain syndrome proton pomp inhibitors (PPIs) and Histamine2-blockers (H2-blockers) are recommended to use (IPPs and H2-blockers were described above).

Psychotropic drugs, especially antidepressants, are often used as second-line drugs in functional gastrointestinal disorders.

Psychological therapies are advocated as rescue therapy for FD symptoms that are severe and not responding to pharmacotherapy.

Materials for self-control:

A. Tests and situational tasks for self-control:

1. PPIs include:

A) famotidine

B) itopride

C) pantoprazole

D) clarithromycin

2. H2-blockers include:

A) famotidine

B) itopride

C) pantoprazole

D) clarithromycin

3. Prokinetics include:

A) famotidine

B) itopride

C) pantoprazole

D) clarithromycin

4. Standard dosage of Pantoprazole is:

A) 20 mg

B) 60 mg

C) 40 mg

D) 20-40 mg

B. Situational tasks for self-control:

5. A 39-year-old man complains of occasional difficulties in swallowing of both hard and fluid food for many months. Sometimes he feels intense pain behind his breast bone, epecially after hot drinks. There are asphyxia onsets at night. He doesn't have weight loss. PE: his general condition is satisfactory; skin is pale-pink. Examination revealed no pathological signs of gastrointestinal tract. X-ray picture of thorax organs presents esophagus dilatation with level of fluid in it. What is the preliminary diagnosis?

A) Myastenia

B) Esophagus achalasia

C) Cancer of esophagus

D) Esophagus candidosis

E) Gastroesophageal reflux

6. A 37-year-old patient complains of discomfort in epigastrium, especially after stress, and occasional heartburn. These symptoms were present when patient was in his teens. Patient doesn't experience nausea, vomiting or weight loss. Objectively: a belly is painless on palpation, the liver and spleen are not enlarged. What is the probable preliminary diagnosis? What additional tests are necessary for the patient? Make the treatment plan.

Answers: 1-C, 2-A, 3-B, 4-C, 5-B, 6-functional dyspepsia, epigastric pain syndrome. No examination is necessary as the patient does not have alarm symptoms and all

complains suit the diagnosis. HP tests may be done. Treatment options include PPIs e.g. Lansoprazole 30 mg bid 40 minutes before the meal.

Recommended literature

I. Main:

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.
3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічнадіяліків – SideEffectsofMedications: навчальнийпосібнику 2 т. / зазаг.ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

II. Additional literature:

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.

6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143 .
7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).