



**Internal Medicine: in 2 books.
Book 2. Diseases of the
Digestive System, Kidney,
Rheumatic and Hematological
Diseases: textbook**

Про книгу

This textbook describes modern data on epidemiology, the concept of etiology and pathogenesis, clinical features, diagnostics, treatment and prevention of diseases of internal organs.  This book combining European experience with current management and healthcare recommendations, adapted to the credit-module system and the principles of evidence-based medicine, is a modern highly informative, professionally oriented publication.  For students, interns, residents, doctor-cadets of higher medical educational establishments, physicians, specialists of secondary and tertiary medical care.

Nestor M. SEREDYUK, MD, Professor

TEXTBOOK

Internal Medicine

IN 2 BOOKS

BOOK 2

Diseases of the Digestive System, Kidney, Rheumatic and Hematological Diseases

RECOMMENDED

by the Ministry of Health of Ukraine as a textbook
for students and interns of higher medical
educational establishments

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Chapter III

DISEASES OF THE DIGESTIVE SYSTEM

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux (GER) is a normal physiological process, and it can occur in up to 70 % of completely healthy newborns and infants. The GER resolves spontaneously in 95 % of the individuals up to 12–14 months of age. If GER causes troublesome symptoms and/or complications, the diagnosis of GERD can be considered.

The term “gastroesophageal reflux disease” (GERD) has appeared relatively recently and to some extent replaced the previous name “reflux esophagitis” and “reflux disease”. While these terms are synonymous, the new name — “gastroesophageal reflux disease” is more complete, as it includes a typical combination of symptoms caused by the throwing of acidic gastric contents into the esophagus. This is important not only for throwing, but also to the ability of the esophagus to become relaxed, cleansed from such a stimulus. This phenomenon is called *esophageal clearance*. It is believed that in the normal clearance of the esophagus, the rare throwing cannot cause gastroesophageal reflux disease. In the case of reduction of esophageal clearance in response to the periodic throw-out of acidic stomach contents into the esophagus, the mucous membrane becomes inflamed quickly. The decrease in the lower esophageal obturator tone due to the frequent development of gastric failure in this disease is also of great importance. *Gastrin* is the important hormone of the stomach; it performs a general trophic function, regulates the tone of sphincters and gastric secretion. In the case of peptic ulcer, mechanism of gastrin formation is broken, and reflux esophagitis develops, as a rule, in most of the patients. Today the mechanism of gastroesophageal reflux disease including the role of nitric oxide has been clarified.

Most clinicians treat gastroesophageal reflux disease as damage of varying severity degree of the mucous lining of the distal part of the esophagus, accompanied by characteristic clinical symptoms and pathological results from continuous casting (reflux) of gastric and duodenal contents into the lumen of the esophagus.

Etiology and Pathogenesis. According to modern concepts, gastroesophageal reflux disease is considered as a consequence of dysmotility of the esophagus and stomach. In the development of gastroesophageal reflux disease, the key importance is played by the reduction of antireflux barrier, lowering of the tone of the lower esophageal sphincter and esophageal clearance, increase in episodes (frequency) of its relaxation, and increase in the intragastric pressure. Additional factors that create conditions for the development of gastroesophageal reflux disease are aggressive components of gastric juice (hydrochloric acid, pepsin, bile acids, pancreatic enzymes — trypsin and phospholipase A₂) against the reduced resistance of the esophageal epithelium. Gastroparesis, decrease in saliva production (Sjogren’s disease), impairment of cholinergic innervations of the esophagus are also important. The microorganisms *Helicobacter pylori* play a special role in the development of gastroesophageal reflux disease.

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Drinks containing caffeine (coffee, tea, cocoa, Coca-Cola, and Pepsi-Cola), juices, oranges, lemons, grapefruit, alcohol, milk, tomatoes, horseradish, onion, garlic, pepper, and other spices increase the formation of gastric acid and lower the tone of the lower esophageal sphincter.

According to the classification of A.P. Peleshchuk and his co-authors (1995), gastroesophageal reflux disease should be distinguished from secondary reflux esophagitis observed in peptic ulcer, hiatal hernia, after gastric surgery, in scleroderma, in esophageal cancer, and so on.

The majority of patients with abnormal gastroesophageal reflux during the daytime and night-time monitoring have the pH less than 4.

Clinics and diagnostics: GERD can cause a variety of gastroesophageal (typically heartburn and regurgitation) and extraesophageal symptoms.

The main symptoms of gastroesophageal reflux disease involve the heartburn and regurgitation, which appear at least twice a week at least 4–8 weeks or more, as well as a sense of pressure in the epigastric region arising in 15–40 min after eating and drinking that can be provoked by the use of products stimulating the synthesis of hydrochloric acid by the stomach and bile by the liver (fried, spicy food, juices, alcohol, dry red wine, and carbonated drinks such as Coca-Cola, Pepsi-Cola, Fanta, as well as coffee, chocolate, cocoa, radishes, and vegetable oil in large quantities).

Often the patients with gastroesophageal reflux disease complain of the chest pain radiating to the neck, lower jaw, left shoulder and arm, under the left shoulder blade. In the latter case, the differential diagnosis should be made with coronary artery disease (angina) (Table 3.1).

TABLE 3.1

GERD symptoms

(adapted from Bruley des Varannes et al., 2014)

<i>Typical</i>	Heartburn (daytime or night-time)
	Regurgitation (daytime or night-time)
	Water brush (daytime or night-time)
<i>Atypical</i>	Nausea, eructation (belching)*
	Slow digestion, early satiety*
	Epigastric pain*
	Bloating*
	Vomiting
	Chest pain (precordial)
	Respiratory symptoms (cough, wheeze, chronic rhinosinusitis)
	ENT symptoms (hoarseness, pharyngeal pain, globus)
	Early awakening
Nocturnal awakening, nightmares	

*Can be considered to be associated with GERD if symptoms improve in response to PPI treatment.

The chest pain in cases of gastroesophageal reflux disease can be associated with the consumption of food, including overeating, low head position during sleep, and it can be usually stopped after taking antacidic or alkaline mineral waters, Morshynska No 6, Naf-tusya Truskavetska and Zbruchanska.

The above complaints are usually triggered by exercise, frequent bents, overfullness with liquid, oily, dense and sweet food, alcohol, and they are aggravated at night.

Introduction of esophageal contents into the lumen of the bronchi may cause bronchospasm — bronhoaspirational Mendelson's syndrome (for the lethal outcome it's enough to get 2—4 mL of acidic gastric juice in the bronchial tree).

Patients with GERD can also present with dysphagia, the upper gastrointestinal bleeding, chest pain, and epigastric pain. These symptoms ('red flag' symptoms) indicate a severe acute disease and should be clarified by immediate, relevant diagnostic studies.

Extraesophageal symptoms (EES) include respiratory and oropharyngeal symptoms such as a chronic cough, hoarseness, sore throat and pharyngeal burning. Also, the burning sensation of the tongue and mouth, globus sensation, and dental erosions can be related to GERD. The term *extraesophageal reflux (EER)* is used for respiratory-related symptoms. Although there is no consensus definition of EER, the common sense leads to define EER as related to lesions and/or symptoms caused by gastroesophageal reflux that reaches structures above the upper esophageal sphincter.

During the examination of a patient with gastroesophageal reflux disease, the dry mouth (xerostomia), mushroom-like hypertrophied papillae of the tongue (the result of gastric hypersecretion), positive left or right phrenicus-symptom, and symptoms of laryngitis (voice hoarseness) can be revealed.

The diagnosis of gastroesophageal reflux disease can be radiographically confirmed if there are flowing back (throwing) of the contrast material from the stomach into the esophagus, results of twenty-four hour pH monitoring in the esophagus (with normal pH 5.5—7 pH in patients with GERD for 5 minutes — 1 hour or more is less than 4, or detection of gastroesophageal reflux over 50 cases a day). However, the gold standard for diagnosing the gastroesophageal reflux disease is *the endoscopic method*.

In Europe, there are two most widely used endoscopic classifications of esophagitis in GERD — the Savary and Miller's classification and the Los Angeles Classification (Table 3.2).

Classification of lesions of the esophagus by esophagoscopy according to Savary—Miller is as following:

0 degree. The esophageal mucous membrane is intact.

The Ist degree of severity: some erosions, which do not merge with each other, and (or) erythema of the mucous membrane of the distal part of the esophagus.

The IInd degree of severity: erosions, which merge with each other, but do not apply to the most of the mucous membrane of the distal part of the esophagus.

The IIIrd degree of severity: erosive lesions of the lower third of the esophagus — erosions merge and cover the entire surface of the mucous membrane of the distal part of the esophagus.

The IVth degree of severity: erosive and ulcerative changes or complications: esophageal stricture, bleedings, and mucosal metaplasia with the formation of the endoscopic picture, the so-called "paving", and the formation of Barrett's esophagus.

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Classification of gastroesophageal reflux disease (GERD) (adapted from N.V. Kharchenko, 2015):

I. By the nature of endoscopic changes in the esophagus:

- Non-erosive GERD (endoscopically negative variant, GERD without esophagitis, symptomatic GERD).
- Erosive GERD (reflux-esophagitis, endoscopically positive variant, GERD with esophagitis).

II. Complications of the erosive GERD:

- Peptic ulcer of the esophagus.
- Bleeding.
- Esophageal stricture.

III. Barrett's esophagus (intestinal metaplasia of incomplete type in the distal part of the esophagus):

— By the length of the Barrett's esophagus segment:

- A short segment of the Barrett's esophagus.
- A long segment of the Barrett's esophagus.

— By the Prague criteria*:

• The size of the criterion C: the difference between the depth of the endoscope introduction to the level of circular (C) metaplasia and the distance to the esophageal-gastric junction.

• The size of the criterion M: the difference between the depth of the endoscope introduction to the level of maximum (M) metaplasia and distance to the esophageal-gastric junction.

IV. By the nature of clinical manifestations:

- Typical reflux syndrome.
- Syndrome of the retrosternal reflux pain.
- Extra-oesophageal manifestations of GERD:

— With an established association:

- A chronic cough.
- Reflux laryngitis.
- Asthma.
- Damage to the tooth enamel.

— With a predictable association:

- Pharyngitis.
- Sinusitis.
- Recurrent media otitis.
- Idiopathic pulmonary fibrosis.
- Refractory GERD.

* Determination of Prague criteria. At first it's needed to determine the esophageal-gastric junction (EGJ) by the depth of endoscope introduction — to the tops of folds of the mucous membrane of the stomach and cardiac sphincter, for example 36 cm. Then the presence of visible "tongues of flame" of metaplasia above EGJ is established, and the depth of endoscope introduction to the level of the proximal edge of the circular metaplasia (e.g., 22 cm) and maximal metaplasia (e.g., 30 cm) is determined. The difference between the depth of the endoscope introduction to the circular (C) metaplasia zone and distance to EGJ is the value of the criterion C (36 cm — 30 cm = C6). The difference between the depth of the introduction of the endoscope to the maximum (M) metaplasia zone and distance to EGJ is the value of the criterion M (36 cm — 22 cm = M14). In this case, Prague criteria will be described as C6 and M14.

TABLE 3.2

The Los Angeles Classification of Esophagitis (1998)

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 (see colour Fig. 3.1 a; 3.1 b; 3.1 c; 3.1 d)

Another important diagnostic tool is pH monitoring or impedance pH monitoring, which is necessary to objectively document pathologic acid exposure and/or other pathologic reflux activities. Impedance-pH monitoring increases the diagnostic value of these functional studies by quantifying acid and non-acid reflux and by providing a correlation between the symptoms and documented reflux episodes. Also, esophageal pH monitoring has an important prognostic value in patient selection for the antireflux surgery. Esophageal manometry is not important in establishing the diagnosis of GERD. It does, however, have some value as a marker of severity of the disease in that LES incompetence is associated with a more severe disease and long-term course. Manometry studies are important before any surgical procedure to evaluate motility disorders, especially spastic motility disorders or achalasia.

Dynamic barium sandwich videography is important in evaluating patients with dysphagia. In cases of large hernias, the barium study can provide information about the possibility of the short esophagus. In GERD patients with nausea and vomiting as the major complaints, the gastric emptying studies and duodenogastroesophageal reflux assessment should be done to evaluate the presence of gastroduodenal motility disorder such as the delayed gastric emptying.

There are the following recommendations for *the GERD diagnosis* according to ACG:

- A suggested diagnosis of GERD can be established with typical symptoms of heartburn and regurgitation. Empiric medical therapy with a proton pump inhibitor (PPI) is recommended (Strong recommendation, moderate level of evidence).
- Patients with the non-cardiac chest pain suspected due to GERD should have a diagnostic evaluation before the institution of therapy (Conditional recommendation, moderate level of evidence). A cardiac cause should be excluded in patients with the chest pain before the commencement of gastrointestinal evaluation (Strong recommendation, low level of evidence).
- Barium radiographs should not be performed to diagnose GERD (Strong recommendation, high level of evidence).
- Upper endoscopy is not required in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and for the screening of patients at high risk of complications. Repeated endoscopy is not indicated for patients without Barrett's esophagus in the absence of new symptoms (Strong recommendation, moderate level of evidence).

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- Routine biopsies from the distal esophagus are not recommended to diagnose GERD specifically (Strong recommendation, moderate level of evidence).

- Esophageal manometry is recommended for preoperative evaluation, but doesn't matter in the diagnosis of GERD (Strong recommendation, low level of evidence).

- The ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy for the patients with the non-erosive disease, as part of the evaluation of the patients' refractory to PPI therapy, and in cases, when the diagnosis of GERD is doubtful. (Strong recommendation, low level of evidence). Ambulatory reflux monitoring is the only test that can assess reflux symptom association (Strong recommendation, low level of evidence).

- Ambulatory reflux monitoring is not required in the presence of short or long-segment Barrett's esophagus to establish the diagnosis of GERD (Strong recommendation, moderate level of evidence).

- Screening for *Helicobacter pylori* infection is not recommended for GERD patients. The treatment of *H. pylori* infection is not routinely required as part of antireflux therapy (Strong recommendation, low level of evidence). The more atypical symptoms are present in a certain patient, the more detailed diagnostic assessment should be performed before surgery (to detect all functional defects).

Diagnostic Criteria (Ministry of Health of Ukraine order No 271 dated 13.06.2005) in the case of GERD suspicion:

- Typical clinical symptoms: heartburn and acidic regurgitation.
- Test with proton pump inhibitor: efficacy of the 5–7-day course of application (ex juvantibus) of modern proton pump inhibitors (esomeprazole, rabeprazole, pantoprazole).

- Endoscopic confirmation of esophagitis (see colour Fig. 3.2).

- Positive results of 24-hour esophageal pH-monitoring (pH less than 4, the duration at least 5 minutes in a row).

Additional methods of diagnostics (Fig. 3.3):

- General blood test and biochemical examination of blood.

- *Helicobacter pylori* urea breath test.

- Biopsy (performed if endoscopy shows the suspicion of intestinal metaplasia appears, in patients with ulcerative lesion of the esophagus and/or its stenosis, in suspicion of non-reflux esophagitis etiology).

GERD should be differentiated from a diaphragmatic hernia (X-ray examination in Trendelenburg position; Fig. 3.4), diverticulum of esophagus (the contrast X-ray examination; esophagogastroduodenoscopy; Fig. 3.5), aortic dissection (MSCT, Doppler sonography), pulmonary thromboembolism (D-dimers, Doppler sonography, pulmonary angiography), sarcoidosis (X-ray examination, CT, MRI), CAD (ECG, troponins).



Fig. 3.3. Roentgenogram in gastroesophageal reflux

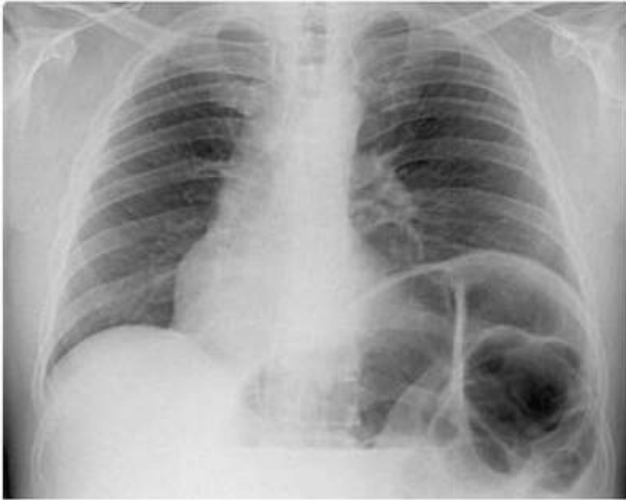


Fig. 3.4. Diaphragmatic hernia



Fig. 3.5. Esophageal diverticulum

Treatment. GERD both erosive and non-erosive is associated with significant impairment of the quality of life. Thus, the goal of medical therapy in GERD is to control the heartburn, to heal gastroesophageal mucosal injuries and to improve the quality of life.

There are the following recommendations for GERD management according to ACG:

- Weight loss is recommended for GERD patients who are overweight or have had recent weight gain (Conditional recommendation, moderate level of evidence).
- The head of bed elevation and avoidance of meals 2–3h before bedtime should be recommended for patients with nocturnal GERD (Conditional recommendation, low level of evidence).
- Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and/or spicy food) is not recommended in the treatment of GERD (Conditional recommendation, low level of evidence).
- An 8-week course of PPIs is the therapy of choice for the symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs (Strong recommendation, high level of evidence).
- Traditional delayed-release PPIs should be administered 30–60min before a meal for maximal pH control (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal-timing (Conditional recommendation, moderate level of evidence).
- PPI therapy should be initiated at once a day dosing, before the first meal of the day (Strong recommendation, moderate level of evidence). For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and/or twice daily dosing should be considered for patients with night-time symptoms, variable schedules, and/or sleep disturbances (Strong recommendation, low level of evidence).
- Non-responders to PPI should be referred for evaluation (Conditional recommendation, low level of evidence, see refractory GERD section).

CHAPTER III. DISEASES OF THE DIGESTIVE SYSTEM

- For the patients with partial response to PPI therapy, increase in the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief (Conditional recommendation, low-level evidence).
- Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after discontinuation of PPI, and for patients with complications including erosive esophagitis and Barrett's esophagus (Strong recommendation, moderate level of evidence). For the patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on-demand, or intermittent therapy (Conditional recommendation, low level of evidence).
- H₂-receptor antagonist (H₂RA) therapy can be used as a maintenance option for the patients without erosive disease if patients experience heartburn relief (Conditional recommendation, moderate level of evidence). Bedtime H₂RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphylaxis after several weeks of use (Conditional recommendation, low level of evidence)
- Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used for GERD patients without diagnostic evaluation (Conditional recommendation, moderate level of evidence).
- There is no role for Sucralfate for the non-pregnant GERD patient (Conditional recommendation, moderate level of evidence).
- PPIs are safe for pregnant patients if clinically indicated (Conditional recommendation, moderate level of evidence).
- Surgical therapy is a treatment option for long-term therapy for the patients with GERD (Strong recommendation, high level of evidence).
- Surgical therapy is generally not recommended for patients who do not respond to PPI therapy (Strong recommendation, high level of evidence).
- Preoperative ambulatory pH monitoring is mandatory for the patients without evidence of erosive esophagitis. All patients should undergo the preoperative manometry to exclude achalasia or scleroderma-like esophagus (Strong recommendation, moderate level of evidence).
- Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by a skillful surgeon (Strong recommendation, high level of evidence).
- Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation for these patients (Conditional recommendation, moderate level of evidence).
- The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy (Strong recommendation, moderate level of evidence).
- PPI therapy can be a risk factor for *Clostridium difficile* infection and should be carefully used for patients at risk (Moderate recommendation, moderate level of evidence).
- Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not increase in long-term users (Conditional recommendation, moderate level of evidence).
- PPI therapy should not be altered with concomitant clopidogrel users, as there is no increased risk of adverse cardiovascular events (Strong recommendation, high level of evidence).

- GERD can be considered as a potential co-factor in patients with asthma, chronic cough or laryngitis. Careful evaluation for non-GERD causes should be undertaken for all of these patients (Strong recommendation, moderate level of evidence).

- A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD (Strong recommendation, low level of evidence).

- The first step in the management of refractory GERD is optimization of PPI therapy (Strong recommendation, low level of evidence).

- The upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies (Conditional recommendation, low level of evidence).

- In patients with extraesophageal symptoms of GERD, in spite of PPI optimization, other etiologies should be evaluated by an attendant assessment of ENT, pulmonary and allergic examination (Strong recommendation, low level of evidence).

- Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery or TLESR inhibitors (Conditional recommendation, low level of evidence). Patients with negative testing are unlikely to have GERD, and PPI therapy should be discontinued (Strong recommendation, low level of evidence).

- Continuous PPI therapy is recommended the following peptic stricture dilation to improve dysphagia and reduce the need for repeated dilations (Strong recommendation, moderate level of evidence).

- Injection of intralesional corticosteroids can be used in refractory, complex strictures due to GERD (Conditional recommendation, low level of evidence).

- The PPI treatment is suggested after dilation in patients with lower esophageal (Schatzki) rings (Conditional recommendation, low level of evidence).

- Screening for Barrett's esophagus should be considered in patients with GERD who are at high risk based on the epidemiologic profile (Conditional recommendation, moderate level of evidence).

- Symptoms in patients with Barrett's esophagus can be treated in a similarly to patients with GERD who do not have Barrett's esophagus (Strong recommendation, moderate level of evidence).

- Patients with Barrett's esophagus found at endoscopy should undergo periodic surveillance according to guidelines (Strong recommendation, moderate level of evidence).

The most important condition for the treatment is the life style alteration — the smoking cessation, stop using alcohol, weight loss, avoiding the horizontal position of the body after meals and at bedtime, refusal to wear corsets, bandages — anything that increases the intraabdominal pressure. The regime and the character of the diet has to be changed, too: avoid overeating, eating at night, lying down after eating; withdrawal from the diet food rich in fats (milk, cream, goose, duck, pork, lamb), as well as coffee, tea, Coca-Cola, citrus, tomatoes, garlic, and dry red wines.

Antacids are well tolerated, safe, and effective in reducing heartburn and controlling acid regurgitation (typical symptoms of GERD) in patients with the mild reflux disease.

Acid-suppressive medicines are safe and effective in patients with esophageal syndromes. Proton pump inhibitors (PPIs) are more effective than H₂ receptor antagonists in providing mucosal healing and symptomatic relief.

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