

Gastroesophageal Reflux Disease (GERD, Acid Reflux) and Barrett's Esophagus — Diagnosis and Treatment

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Gastroesophageal reflux disease and its complications, particularly Barrett's esophagus, is a much favored exam topic. Due to its high prevalence amongst the west industrial countries and its increasing incidence, medical students are expected to come across symptoms associated with this condition all the more often in daily clinical practice. That is why you should definitely be well-prepared for such an occasion.



Definition of GERD

Defining terminology related to the reflux disease is something worth taking a careful look at, so that one will not get confused when participating in an exam.

Gastroesophageal reflux

Gastroesophageal reflux is defined as the temporary reflux of gastric content into the [esophagus](#), something that may also occur to healthy individuals. Up to a certain degree, it is a physiological response, particularly after the consumption of a fatty meal or wine.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (= GERD) is sometimes also called **(acid) reflux disease**. The aforementioned reflux leads to a diminished life quality and/or puts the individual's health at risk. It is further divided into:

- **NERD** (non-erosive reflux disease): The patients suffer from an asymptomatic reflux. However, a reflux esophagitis cannot be macroscopically or histologically ascertained.
- **ERD** (erosive reflux disease) = **Reflux esophagitis**: Here, endoscopy will reveal mucosal lesions in patients with reflux disease, either macroscopically or histopathologically. This piece of evidence suffices to diagnose a **reflux esophagitis**.
- **Barrett-esophagus**: A potential **epithelial dysplasia** that can occur in the esophagus during the course of GERD, which constitutes a precancerous stage of an esophageal adenocarcinoma.

Epidemiology of GERD

Reflux disease increases

Up to 20 % of people in west industrial countries are affected by acid reflux disease (increasing incidence), 60 % of whom display no lesions (**NERD**). The remaining 40 % display a reflux esophagitis (**ERD**).

Etiology of GERD

Depending on its etiopathogenesis, reflux disease is divided into the following two categories:

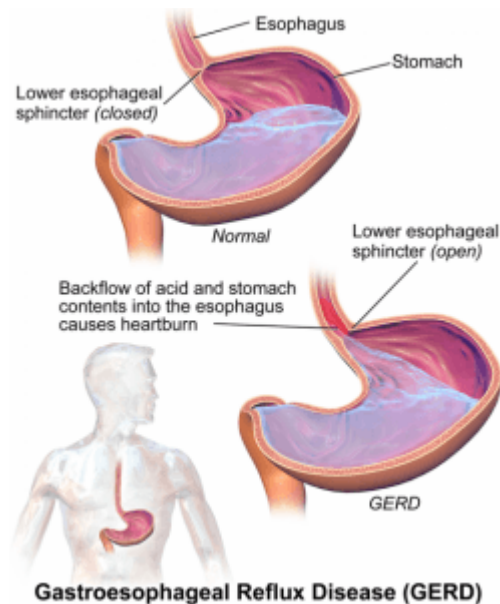
- **Primary reflux disease** (most common type, around 80 - 90 %)
- **Secondary reflux disease**

Causes of primary reflux disease

Prevalent causes include a **primary insufficiency of the lower esophageal sphincter**, as well as an increased production of gastric acid - often of **unknown origin**.

Factors encouraging the development of reflux disease:

- Coffee, smoking, alcohol, heavy evening meal;
- Adipositas (increased intra-abdominal pressure due to obesity);
- Stress;
- Insufficiency of the diaphragmatic crura.



Picture: "GERD" by BruceBlaus. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Reflux patients often suffer from an axial hiatal hernia at the same time. Looking at it the other way around, among patients with a hiatal hernia, the number of those who simultaneously suffer from reflux disease is not significantly higher when compared to patients without a hiatal hernia; that is why the latter seems to play no causal role. However, a hiatal hernia seems to encourage the step from a **gastroesophageal reflux** to a **gastroesophageal reflux disease**.

Causes of secondary reflux disease

A secondary reflux disease arises when there is a determinable underlying condition causing an **esophageal sphincter disorder** or an **aggressive reflux**. For example:

- Female patient during the last months of pregnancy (increased intra-abdominal pressure);
- After an operation to treat achalasia;
- Pyloric stenosis;
- Scleroderma.

Pathophysiology of GERD

Various different factors promote the onset of a reflux disease

In the majority of the cases, various etiological factors primarily result in a **lower esophageal sphincter insufficiency**. Normally, the sphincter functions as a **reflux barrier**. Physiologically, resting pressure in the lower esophageal sphincter approximately amounts to 20 mmHg: As it is higher than the intragastric pressure, it protects from a potential backflow of the stomach's contents into the esophagus. The only time when the esophageal sphincter slackens temporarily is during the swallowing process. An insufficiency can manifest in two ways:

- **Inadequate sphincter relaxation** (during the swallowing process);
- **Generally decreased resting pressure.**

In addition to these, a dysfunctional self-purification of the esophagus (**decreased esophageal clearance**), also leads to a prolonged contact of reflux with the esophagus.

Finally, another fact that is related to the disease's pathophysiology, and must not be omitted, is that the esophageal mucosa is subjected to damage caused by **acidic gastric juices**. An **alkaline biliary reflux** is very rarely the reason behind a reflux disease.

Note: From a pathophysiological aspect, the lower esophageal sphincter insufficiency is crucial.

Symptoms of GERD

Heartburn affects 75 % of the patients

Cardinal symptoms of gastroesophageal reflux disease include:

- **Heartburn** (75 % of the patients);
- Burping (60 % of the patients), also accompanied by bloating;
- **Regurgitation** of food residue, which leaves a sour taste behind;
- **Dysphagia.**

Many patients also describe a certain **thoracic pain** (DD myocardial infarct!). Paroxysmal retrosternal pain is caused by a spasm of the esophageal muscle, which can occur in cases of recurrent reflux. A reflux-induced vagal stimulation can cause a dry cough, whereas some patients also complain of weakness and vomiting.

Note: Symptoms deteriorate with lying, pressure, bending, effort and stress.

Complications of GERD

Mucosal lesions can become ulcerated and form **strictures** and **peptic stenoses** in the lower esophagus. Such a circular stricture can also be named „**Schatzki's Ring.**“

A potential nocturnal **aspiration** of gastric contents can lead to **pneumonia** or **chronic bronchitis**; an asthma can also be provoked or deteriorate. The nocturnal intensified backflow of acid can also lead to **laryngitis** with hoarseness, especially in the morning.

Barrett's esophagus

A dreaded complication of reflux disease is Barrett's esophagus. The multi-layered, non-cornified **squamous epithelium** of the terminal esophagus is damaged by the constant, non-physiologic contact with gastric acids and finally turns into a **columnar epithelium of intestinal type** with goblet cells.

These transformed segments of columnar epithelium follow a proximal, tongue-like course. If they extend to a surface of less than 3 cm, we talk about a **Short-segment-Barrett**. If they exceed the 3 cm length limit, the condition is called **Long-segment-Barrett**. This classification is of vital, first-line prognostic importance.

Barrett's esophagus appears in endoscopy like this:



Picture: “(A) Conventional endoscopic view of Barrett's esophagus with concomitant esophagitis. (B) Positive staining of Barrett's epithelium after absorption chromoendoscopy with methylene blue dye solution (1%, 10 mL). (C) Villous cerebroid pits with finger-like projections seen with magnification endoscopy (pattern 5 according to Endo's classification). (D) Histological section of (C) showing intestinal metaplasia with glands of different size and shape and numerous goblet cells,” by Openi. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Mucosal lesions run out in a tongue-like manner in an irregular Z-line. Histology confirms the suspicion.

Barrett's esophagus, and its epithelial dysplasia, is considered a **precancerosis**, since it provides the substrate on which adenocarcinomas can develop (around 10 % of the cases).

Note: Malignant degeneration risk particularly rises in cases of Long-segment-Barrett.

Differential Diagnosis of GERD

Demarcating reflux disease among other esophageal conditions

Differential diagnosis takes into consideration first of all other **esophageal conditions**, e.g., esophagitis, esophageal cancer, diverticulitis, achalasia or other motility disorders.

Another cause of mucosal esophageal ulcerations is pills (**NSAIDs, doxycycline**, etc.)

Other conditions whose symptoms may resemble those of reflux disease include a [myocardial infarct](#), [coronary heart disease](#) and [gastroduodenal ulcers](#).

Diagnosis of GERD

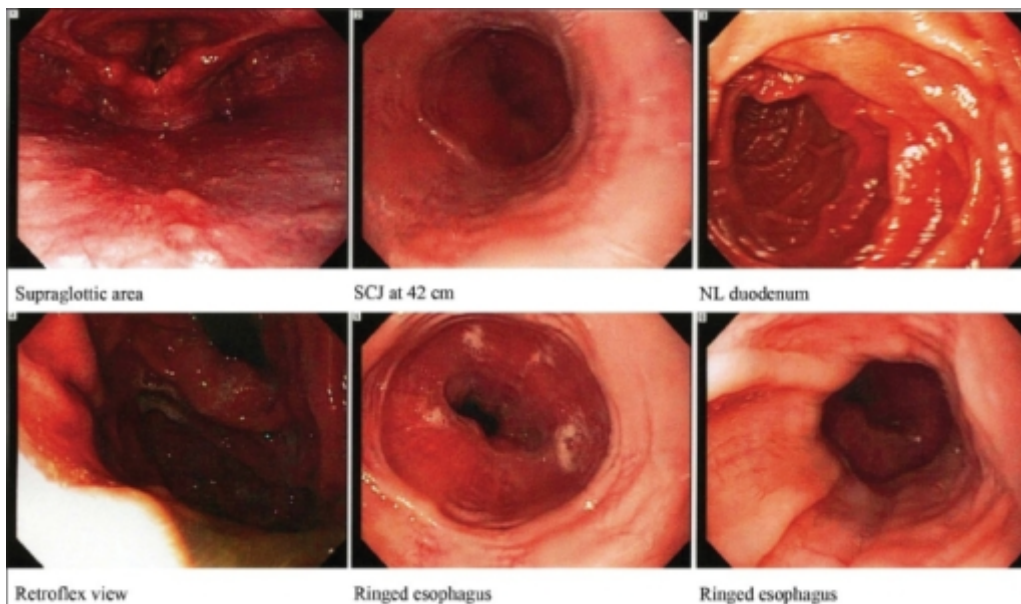
Medical history and PPI treatment of reflux disease

When a patient describes symptoms possibly related to a mild acid reflux disease, first-line treatment with **proton pump inhibitors** can be attempted. Should the patient respond positively to the treatment, the hypothesized diagnosis of reflux disease will be corroborated.

Esophagoscopy with biopsy

In order to confirm a reflux esophagitis and inspect for a possible Barrett's esophagus, an endoscopy is performed, always followed by extraction of biopsy material ("**Four-Quadrant biopsy**"). The endoscopic findings facilitate the classification of reflux esophagitis into categories, depending on its degree of severity (see below).

Endoscopy also helps to exclude other conditions otherwise included in the differential diagnosis: an **esophageal thrush (yeast infection)** presents in white. An **eosinophilic esophagitis** (unknown etiology, but often associated with diseases of the atopic spectrum) stands out with bloody mucosa ("**crêpe-paper**" mucosa) and ring-shaped erosions, sometimes called "feline-esophagus", due to its resemblance to the esophagus of a cat.

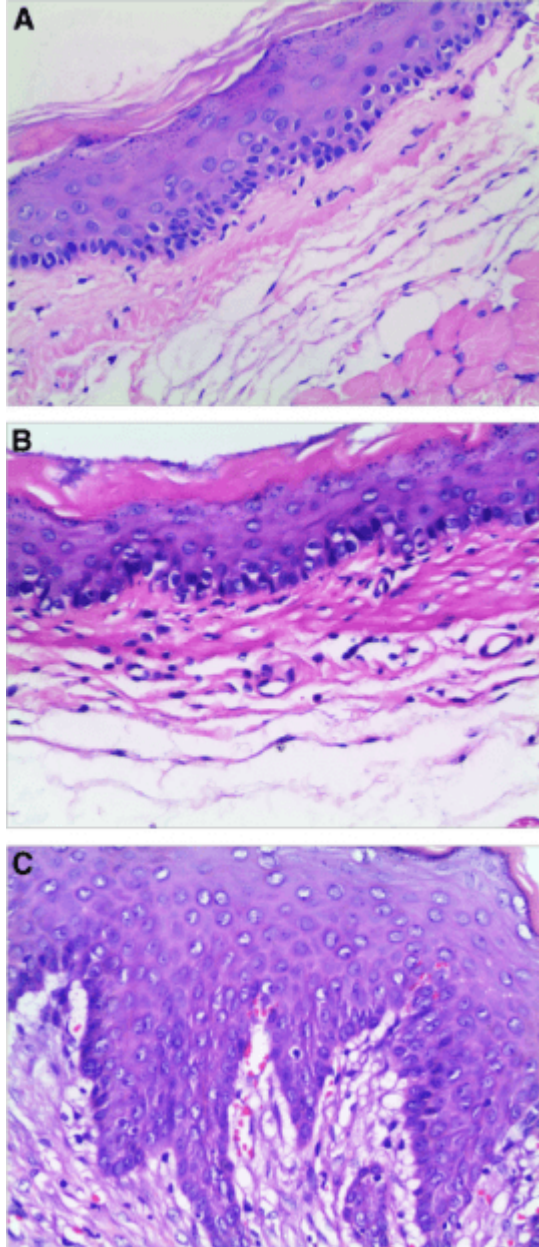


Picture: "Concentric rings in the distal esophagus, consistent with eosinophilic esophagitis," by Openi. License: [CC BY 2.0](#)

In addition to the endoscopy with four-Quadrant biopsies, methods like **chromoendoscopy** with methylene blue, **fluorescence diagnostics** and **magnification endoscopy** can also be performed, in order to diagnose and monitor the disease.

Histology

The biopsies extracted during endoscopy are searched for reflux esophagitis marks. After that, additional information that is obtained includes: **leukocyte** infiltration, **proliferation** of squamous epithelium, **ulcerations** and **cornification**.



Picture: "Histological assessment of the esophageal mucosa (hematoxylin and eosin $\times 200$) from sham operated rats (A) and GER model rats (B, C). Normal esophageal mucosa is shown in A (controls). The absence of esophageal mucosal inflammation is shown in B (NERD). Basal layer thickening, vascular congestion, and infiltration of inflammatory cells, such as eosinophils, are shown in C (reflux esophagitis, RE)." by Openi. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)



Picture: "Micrograph of Barrett's esophagus," by Nephron. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The existence of Barrett's esophagus is indicated by the conversion of the squamous

epithelium into a columnar epithelium with goblet cells.

Histology also makes a further division of Barrett's-related findings possible:

- **Low Grade Intraepithelial Dysplasia (= LGID)**
- **High Grade Intraepithelial Dysplasia (= HGID)**

24-hour pH monitoring with a nasal tube

This method is particularly applied to patients with **NERD**. Esophageal pH is monitored for 24 hours through a nasal esophageal tube and if a pH of ≤ 4 is determined, it corresponds to a reflux of acidic gastric content. In healthy individuals, such episodes are only seen **postprandially** (after a meal) and just for up to 5 minutes. In patients with acid reflux disease, reflux episodes are particularly observed at **night** and after midnight.

Classification of Reflux Esophagitis

As mentioned in the section about esophagoscopy, there are many useful classifications of gastroesophageal reflux disease, depending on the endoscopic findings. We would like to present two of them here, since they are occasionally an exam question:

Savary-Miller classification

Stage	Endoscopic finding
0	Reflux complaints, but no mucosal erosions.
I	Single mucosal erosions (IA: superficial - "red spots", IB: deep, coated with fibrin - "white spots").
II	Longitudinal mucosal erosions along the mucosal folds (IIA: superficial - "red spots", IIB: deep, coated with fibrin - "white spots").
III	Circular confluent mucosal erosions.
IV	Existent complications. e.g., ulcerations, stenoses, epithelial dysplasia, etc.

Los Angeles classification

Stage	Endoscopic finding
A	Erosions have a diameter < 5 mm and are limited to one mucosal fold.
B	Like A but with a diameter > 5 mm.
C	Erosions extend to more mucosal folds, which, however, involve < 75 % of the circumference.
D	Confluent erosions > 75 % of the circumference.

Therapy of GERD

General measures to treat reflux disease

Generally, the therapy of reflux disease should encompass the following supportive measures:

- **Adjustment of dietary habits:** weight loss, avoiding consumption of sour and alcoholic drinks and food, e.g., coffee, salt, wine, tomato sauce, garlic etc, no late meals, no meals containing much fat or sugar, avoiding to recline directly after eating.
- **Avoiding factors that provoke reflux disease:** nicotine, alcohol, sphincter-relaxing medication (e.g., anticholinergics, calcium antagonists, theophylline).
- **Adjustment of sleep habits:** sleeping with the upper part of the body elevated, lying on one's right side.

Treatment with medication: Proton pump inhibitors

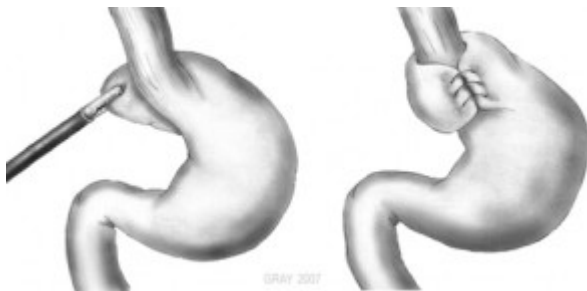
The combination of frequent complaints and esophagitis do make the use of medications necessary: First choice medications include **proton pump inhibitors** (PPI), e.g., **omeprazole** or **pantoprazole**, which suppress gastric acid secretion and help regenerate the mucosa.

Initially, therapy starts with a high dosage (so that already existing erosions will heal more quickly). Maintenance therapy is continued with half the therapeutic dosage (**step-down-treatment**). If the patient relapses after the end of the treatment, a long term prophylactic administration of PPIs in half the standard dosage is applied. In case of occasional relapses, a patient can take PPIs on demand.

H2 receptor antagonists and **antacids** are recommended only in mild cases without signs of inflammation.

Note: Proton pump inhibitors are a first choice therapeutic treatment for acid reflux disease.

Surgical therapy of reflux disease: Nissen fundoplication



Fundoplication Nissen

A laparoscopic **Nissen fundoplication** is indicated for **stage IV**, when conservative methods fail to succeed, when there is an intolerance to proton pump inhibitors or when complications keep occurring (e.g., aspiration pneumonia). Surgical therapy can also be applied to younger individuals who reject a long term PPI treatment.

In a Nissen fundoplication, a **cuff** is **laparoscopically** laid around the lower esophageal sphincter, so as to narrow the cardia and prevent reflux. In order to form the “cuff,” the **fundus** must be mobilized. Eventually, the mobilized fundus is pulled dorsally to the esophagus and is ventrally sewn in place with loose sutures. This method can achieve a subjective freedom from symptoms in up to 80 % of the cases.

A complication that is relatively common and possibly the one asked most often in the exams, is the so-called “**gas-bloat syndrome.**” Patients with reflux disease, who used to swallow air before the operation, continue to do it post-operatively too (disorder is referred to as **aerophagia**). However, a successful fundoplication does not allow for the air to be vented, since the gastroesophageal passage is subjected to a proper pressure ratio. This can lead to nausea, feelings of pressure and even to arrhythmias and a second operation must be performed in order to loosen the cuff.

Control pattern in Barrett’s esophagus

Because of the increased malignant degeneration risk of Barrett’s esophagus, patients

displaying this particular condition are consistently treated and are also frequently observed **endoscopically** with multiple biopsies.

In case of a Barrett's esophagus **without** intraepithelial dysplasia, the patient undergoes two endoscopic controls in one year. If the controls continue to show no degeneration, an interval of 3 (long-segment-Barrett) and 4 (short-segment-Barrett) years is considered to suffice.

In case of a Barrett's esophagus with **LGID** (low grade intraepithelial dysplasia), the patient undergoes two endoscopic controls within the first 6 months. Then the follow up is performed once a year.

In case of a Barrett's esophagus with **HGID** (high grade dysplasia) an **endoscopic mucosal resection** is indicated, or alternatively, a **local radiofrequency ablation (RFA)**.

Prognosis of GERD

Reflux disease is medicinally well curable

In 90 % of the cases, patients are healed of a reflux esophagitis with a PPI therapy. However, if treatment stops, up to 50 % of them relapse!

10 % of patients with reflux disease develop an ulcerative esophagitis. Barrett's esophagus occurs in up to 5 % of GERD-patients and, on its grounds, up to a 10 % of these patients develop an adenocarcinoma.

Review Questions

The answers are below the references.

1. Secondary reflux disease is not likely to be caused by:

- A. A third-trimester pregnancy.
- B. A gastrectomy.
- C. The existence of sclerodermia.
- D. The existence of a carcinoma of the gastric cardia.
- E. A hiatal hernia.

2. A 40-year-old patient undergoes esophagoscopy, where typical signs of a Barrett's esophagus are discovered. A histologic examination of the four-Quadrant biopsies shows no evidence towards a low or high grade dysplasia. Which is the best endoscopic control scheme, considering the intervals?

- A. The patient must be called for endoscopy initially once a year and then, every 5 years.
- B. The patient must present themselves for an endoscopy in case of progressive symptoms.
- C. Initially, two controls within 6 months are indicated and finally every 3-4 years.
- D. The patient must be called once every year for an endoscopic follow-up.
- E. In this case, there is an indication to perform instant endoscopic mucosal resection.

3. To which stage of the usual reflux disease classification do "circular, confluent erosions of the esophageal mucosa" pertain?

- A. Savary and Miller stage III.
- B. Los Angeles classification stage A.
- C. Nissen stage IV.
- D. Stage T1N0M0 according to the criteria of UICC.
- E. None of the above.

References

Freston, J. W. (2001). *Diseases of the gastroesophageal mucosa: The acid-related disorders*. Totowa, NJ: Humana Press.

Mayo Clinic, & Mayo Foundation for Medical Education and Research. (2009). *Reflux and its complications: GERD, Barrett's esophagus and esophageal cancer*.

Shaheen, N. J. (2013). *Benign and neoplastic conditions of the esophagus*. London: Elsevier.

Correct answers: 1E, 2C, 3A

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Notes