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.

Definitions

Gastroesophageal reflux

Gastroesophageal reflux is defined as the temporary reflux of gastric content into the esophagus, and this may also occur in healthy individuals. 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 also called (acid) reflux disease sometimes. GERD leads to diminished life quality and/or puts the individual’s health at risk. GERD is divided into:

- **NERD** (non-erosive reflux disease): The patients suffer from asymptomatic reflux. However, reflux esophagitis cannot be macroscopically or histologically ascertained.
- **ERD** (erosive reflux disease) = Reflex esophagitis: Here, endoscopy will reveal mucosal lesions, either macroscopically or during histopathological examination. This finding is indicative of reflex esophagitis.
- **Barrett-esophagus**: This is potential epithelial dysplasia that can occur in the esophagus during the course of GERD, which constitutes a precancerous stage of esophageal adenocarcinoma.

Epidemiology

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

Etiology

Depending on its etiopathogenesis, reflux disease is divided into the following 2 categories:

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

Causes of primary reflux disease

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

Factors encouraging the development of reflux disease:

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

Patients often suffer from an axial hiatal hernia at the same time. From another viewpoint, 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 progression of gastroesophageal reflux to GERD.

Causes of secondary reflux disease

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

- During the last months of pregnancy (increased intra-abdominal pressure)
After an operation to treat achalasia
- Pyloric stenosis
- Scleroderma

Pathophysiology

Different factors promote the onset of reflux disease

In the majority of the cases, various etiological factors primarily result in lower esophageal sphincter insufficiency. Normally, the sphincter functions as a reflux barrier. Physiologically, the resting pressure in the lower esophageal sphincter approximately is 20 mmHg. As this pressure is higher than the intragastric pressure, it prevents 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. Insufficiency can manifest in 2 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 prolonged contact of the reflux with the esophagus.

Finally, another fact that is related to the disease’s pathophysiology and which is crucial, is that the esophageal mucosa is subjected to damage caused by acidic gastric juices. Alkaline biliary reflux is very rarely the reason behind reflux disease.

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

Symptoms

Heartburn affects 75% of patients

Cardinal symptoms of gastroesophageal reflux disease include:

- Heartburn (75% of 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 (differential diagnosis: myocardial infarction). Paroxysmal retrosternal pain is caused by a spasm of 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

In 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; 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 Barret’s esophagus. The multilayered, non-cornified squamous epithelium of the terminal esophagus is damaged by the constant, non-physiologic contact with gastric acids and finally turns into an intestinal-type columnar epithelium 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, it is a short-segment-Barrett. If they exceed the 3 cm length limit, the condition is called long-segment-Barrett. This classification is of vital prognostic importance.

Barrett’s esophagus appears in endoscopy as in the images below:

- Picture: (A) Conventional endoscopic view of Barrett’s esophagus with concomitant esophagitis. (B) Positive staining of Barrett’s epithelium after absorption chemoendoscopy 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 sizes and shapes and numerous goblet cells. By: Openi. License: CC 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 are considered precancerous since they provide the substrate on which adenocarcinomas can develop (around 10% of the cases).

**Note:** The risk of malignant degeneration particularly rises in cases of long-segment-Barrett.

Differential Diagnosis

Demarcating reflux disease among other esophageal conditions

Differential diagnosis first takes into consideration 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.
Medical history and use of proton pump inhibitors (PPI) for reflux disease

When a patient describes symptoms possibly related to a mild acid reflux disease, first-line treatment with PPI 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 reflux esophagitis and inspect for a possible Barrett’s esophagus, an endoscopy should be performed, always followed by the extraction of biopsy material (‘Four-Quadrant biopsy’). The endoscopic findings facilitate the classification of reflux esophagitis into categories, depending on the degree of severity (see below).

Endoscopy also helps to exclude other conditions otherwise included in the differential diagnosis: an esophageal thrush (yeast infection) has a whitish appearance. 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.

Histology

The biopsies extracted during endoscopy are searched for features of reflux esophagitis. After that, additional information that is obtained includes leukocyte infiltration, the proliferation of squamous epithelium, ulcerations, and cornification.
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-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 the 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 GERD, depending on the endoscopic findings. We would like to present 2 of them here since they are occasionally exam questions:

Savary-Miller classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Endoscopic finding</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Reflux complaints, but no mucosal erosions</td>
</tr>
<tr>
<td>II</td>
<td>Longitudinal mucosal erosions along the mucosal folds (IIA: superficial – ‘red spots’, IIB: deep, coated with fibrin – ‘white spots’)</td>
</tr>
<tr>
<td>III</td>
<td>Circular confluent mucosal erosions</td>
</tr>
<tr>
<td>IV</td>
<td>Existent complications. e.g., ulcerations, stenoses, epithelial dysplasia, etc.</td>
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Los Angeles classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Endoscopic finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Erosions have a diameter &lt;5 mm and are limited to one mucosal fold</td>
</tr>
<tr>
<td>B</td>
<td>Like A but with a diameter &gt;5 mm</td>
</tr>
<tr>
<td>C</td>
<td>Erosions extend to more mucosal folds, which, however, involve &lt;75% of the circumference</td>
</tr>
<tr>
<td>D</td>
<td>Confluent erosions &gt; 75% of the circumference</td>
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GERD Therapy

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., avoiding late meals, avoiding 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: PPIs

The combination of frequent complaints and esophagitis makes the use of medications necessary: first-choice medications include PPIs, 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 comprising 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:** PPIs are the first-choice therapeutic treatment for acid reflux disease.

**Surgical therapy for reflux disease: Nissen fundoplication**

A laparoscopic **Nissen fundoplication** is indicated for **stage IV** when conservative methods fail to succeed when there is an intolerance to PPIs or when complications keep occurring (e.g., aspiration pneumonia). Surgical therapy can also be applied to younger individuals who reject 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 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 so post-operatively (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 arrhythmias and a second operation must be performed in order to loosen the cuff.

**Control pattern in Barrett’s esophagus**

Because of the increased risk of malignant degeneration in Barrett’s esophagus, patients displaying this particular condition are consistently treated and are also frequently observed **endoscopically** with multiple biopsies.

In case of Barrett’s esophagus **without** intraepithelial dysplasia, the patient undergoes 2 endoscopic controls in 1 year. If the results 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 Barrett’s esophagus with LGID, the patient undergoes 2 endoscopic controls within the first 6 months. Then the follow up is performed once a year.

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

Prognosis of GERD

Reflux disease is curable

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

Ten percent of patients with reflux disease develop ulcerative esophagitis. Barrett’s esophagus occurs in up to 5% of GERD patients and up to 10% of these patients develop an adenocarcinoma.

Review Questions

The answers can be found below the references.

1. Secondary reflux disease is not likely to be caused by:
   A. Third-trimester pregnancy
   B. Gastrectomy
   C. Scleroderma
   D. Carcinoma of the gastric cardia
   E. Hiatal hernia

2. A 40-year-old patient undergoes esophagoscopy, where typical signs of Barrett’s esophagus are discovered. A histologic examination of the four-Quadrant biopsies shows no evidence of low or high-grade dysplasia. Which is the best endoscopic scheme, considering the intervals?
   A. The patient must undergo endoscopy initially once a year and then, every 5 years
   B. The patient must present themselves for endoscopy in case of progressive symptoms
   C. Initially, two endoscopic controls within 6 months are indicated and finally every 3–4 years
   D. The patient must undergo endoscopic follow-up once every year
   E. In this case, there is an indication to perform instant endoscopic mucosal resection

3. At what stage of the usual reflux disease classification can “circular, confluent erosions of the esophageal mucosa” be found?
   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


**Correct answers:** 1E, 2C, 3A

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