Refractory Gastroesophageal Reflux Disease
Definition & Etiology

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Despite treatment with proton pump inhibitors (PPIs), some patients with gastroesophageal reflux disease (GERD) continue to have reflux symptoms or endoscopic evidence of esophagitis.

The definition of refractory GERD is controversial .

According to most experts, patients with GERD who exhibit partial or lack of response to PPI twice daily are considered to have failed PPI therapy.

GERD in these patients is termed refractory GERD.



However, we suggest that lack of satisfactory symptomatic response to PPI once a day should be considered a failure of PPI therapy.

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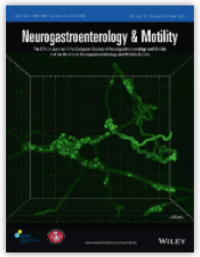

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POSITION PAPER

ESNM/ANMS consensus paper: Diagnosis and management of refractory gastro-esophageal reflux disease

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References Related Information

Recommended

Reflux injury of esophageal mucosa: experimental studies in animal models of esophagitis, Barrett's esophagus and esophageal adenocarcinoma

Yan Li, Robert C. G. Martin

Diseases of the Esophagus

Partial PPI response Partial PPI response, according to the Montreal Consensus, is presence of mild heartburn and/or regurgitation on ≥3days/week despite at least 4 weeks of PPI.

The term “refractory GERD” has been used loosely in the literature!!

A distinction should be made between refractory symptoms (ie, symptoms may or may not be GERD-related), refractory GERD symptoms (ie, persisting symptoms in patients with proven GERD, regardless of relationship to ongoing reflux), and refractory GERD (ie, objective evidence of GERD despite adequate medical management).

The present ESNM/ANMS consensus paper proposes use the term “refractory GERD symptoms” only in patients with persisting symptoms and previously proven GERD by either endoscopy or esophageal pH monitoring.

The term “refractory GERD symptoms” refers to the persistence of symptoms on therapy in patients with prior objective evidence of GERD (erosive esophagitis, peptic stricture, long segment Barrett's esophagus, or abnormal esophageal acid exposure on reflux monitoring performed off therapy).

Refractory reflux-like symptoms are more likely to be reported by:

- Females
- Low BMI
- With dyspepsia and/ or IBS
- With nighttime symptoms
- With sleep disturbances

Refractory GERD symptoms are not associated with presence or absence of Helicobacter pylori

What are the etiologies of refractory GERD ?



Insufficient acid suppression

A range of mechanisms can result in insufficient suppression of gastric acid.

Medication related factors Medication timing and adherence

Poor compliance with PPI timing and adherence is an important cause for inadequate acid suppression and refractory GERD.

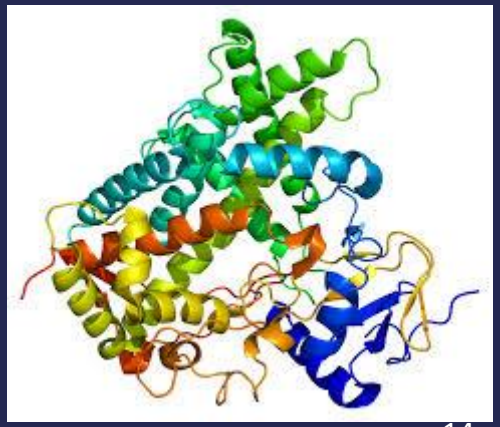
PPIs should be administered 30 to 60 minutes before breakfast for maximal inhibition of proton pumps.



Differences in PPI metabolism

PPIs are metabolized through hepatic cytochrome system, with CYP2C19 having dominant role.

The activity of CYP2C19 is determined to some extent by a genetic polymorphism.



Approximately 5% of White patients and >10% of Asian patients are homozygous for a CYP2C19 mutation (slow metabolizers), potentially leading to greater suppression of gastric acidity.

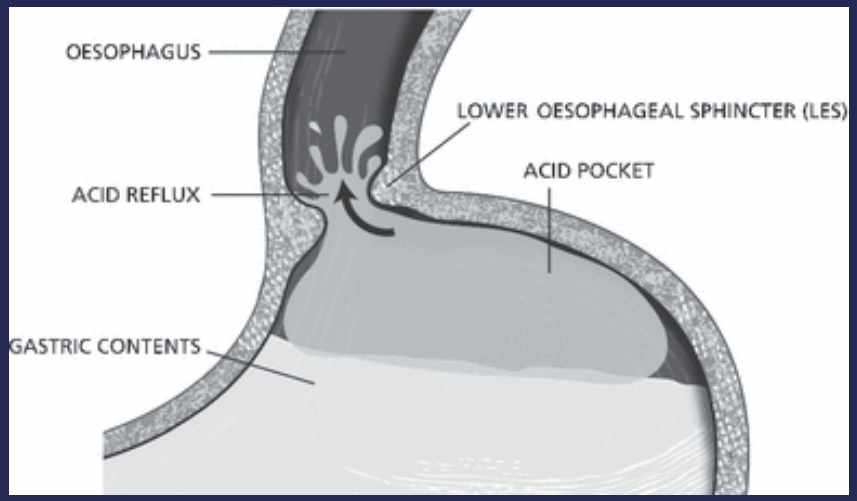
However, in wild type homozygotes (rapid metabolizers) the effect of PPIs on gastric acidity is diminished and may contribute to PPI failure.

Residual acid reflux

Residual acid reflux has been documented in patients despite PPI therapy, however, the incidence in patients on twice daily therapy is low .

What do you remember from “Acid Pocket” term?

Presence of concentrated, highly acidic gastric juice postprandially at gastroesophageal junction, termed **acid pocket**, likely has a limited role in refractory GERD by causing re-reflux of gastric acid.



Weakly acidic or alkaline reflux (non-acid reflux)

Non-acid reflux episodes primarily occur in postprandial period as transient lower esophageal sphincter relaxation occurs more frequently following meal-induced gastric fundus distension.

In patients on PPIs, treatment changes acidity of the refluxate but does not decrease volume of reflux or affect structural and motility abnormalities at the gastroesophageal junction responsible for GERD.

In patients not on acid suppressive therapy, non-acid reflux results when gastric acid is buffered by the ingested food in postprandial period.

Reflux hypersensitivity

Reflux hypersensitivity is characterized by retrosternal symptoms, including heartburn and chest pain associated with non-pathologic acid exposure .

In patients with esophageal hypersensitivity, proximal migration of weakly acidic reflux and presence of gas in refluxate are pivotal for symptom generation .

There are limited data on the prevalence of reflux hypersensitivity.

According **to Rome IV criteria**, a diagnosis of reflux hypersensitivity requires all of the following criteria be fulfilled for last 3 months with symptom onset at least 6 months prior to the diagnosis

- Retrosternal symptoms including heartburn or chest pain
- Normal endoscopy and absence of evidence that eosinophilic esophagitis is the cause for symptoms
- Absence of major esophageal motor disorders
- Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH–impedance monitoring

Functional heartburn

Functional heartburn is among most common cause for failure of PPI treatment.

It is estimated that up to 58 percent of patients with persistent heartburn despite PPI therapy have functional heartburn .

According to Rome IV criteria, a diagnosis of functional heartburn requires all of following criteria be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis :

- Burning retrosternal discomfort or pain
- Absence of symptom relief despite optimal antisecretory therapy
- Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis are the cause of symptoms
- Absence of major esophageal motor disorders

Alternative diagnoses

Other diseases that can mimic symptoms of GERD include

- Achalasia
- eosinophilic esophagitis
- infectious esophagitis
- pill esophagitis
- gastroparesis
- esophageal stricture
- cancer

Rumination syndrome may also be misdiagnosed as GERD.

Refractory GERD can be distinguished from these conditions by diagnostic testing.

Patients with functional dyspepsia commonly also complain of heartburn which may be misdiagnosed as refractory GERD .

Bile reflux may have a role in a subset of patients with difficult to manage symptomatic reflux.

In summary,etiologies include:

Insufficient Acid Suppression/Increased Reflux

- PPI compliance
- PPI timing
- CYP2C19 polymorphism
- Weakly acidic reflux or nonacid reflux
- Nocturnal acid breakthrough
- Missed GERD
- Acid pocket
- Duodenogastroesophageal reflux

Functional Disorders

Alternative Diagnoses Unrelated to GERD

- Zollinger-Ellison syndrome
- Pill-induced/Infectious esophagitis
- Caustic esophagitis
- Radiation-induced esophagitis
- Eosinophilic esophagitis
- Esophageal cancer
- Achalasia
- Gastroparesis
- Helicobacter pylori carrier status
- Rumination syndrome

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Refractory Gastroesophageal Reflux Disease: Diagnosis and Management

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Persistent esophageal symptoms despite seemingly adequate acid suppressive therapy is the starting point for evaluation to determine if GERD evidence exists.

Refractory GERD is diagnosed when abnormal reflux metrics persist on endoscopy and/or pH impedance monitoring performed on optimized GERD therapy in patients with previously proven GERD.

