

## Management of gastro-esophageal reflux disease: Practice-oriented answers to clinical questions

Leonardo Frazzoni, Lorenzo Fuccio, Rocco Maurizio Zagari

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**Leonardo Frazzoni, Lorenzo Fuccio, Rocco Maurizio Zagari**, Department of Digestive Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico S Orsola, Bologna 40138, Italy

**Lorenzo Fuccio, Rocco Maurizio Zagari**, Department of Medical and Surgical Sciences, University of Bologna, Bologna 40138, Italy

**Corresponding author:** Leonardo Frazzoni, MD, Academic Fellow, Medical Assistant, Department of Digestive Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico S Orsola, Via Albertoni 15, Bologna 40138, Italy. [leonardo.frazzoni@gmail.com](mailto:leonardo.frazzoni@gmail.com)

### Abstract

Gastro-esophageal reflux disease (GERD) is a condition which is frequently faced by primary care physicians and gastroenterologists. Improving management of GERD is crucial to maximise both patient care and resource utilization. In fact, the management of patients with GERD is complex and poses several questions to the clinician who faces them in clinical practice. For instance, many aspects should be considered, including the appropriateness of indication to endoscopy, the quality of the endoscopic examination, the use and interpretation of ambulatory reflux testing, and the choice and management of anti-reflux treatments, *i.e.*, proton-pump inhibitors and surgery. Aim of the present review was to provide a comprehensive update on the clinical management of patients with GERD, through a literature review on the diagnosis and management of patients with GER symptoms. In details, we provide practice-oriented concise answers to clinical questions, with the aim of optimising patient management and healthcare resource use.

**Key Words:** Gastro-esophageal reflux disease; Diagnosis; Management; Proton-pump inhibitor

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**Core Tip:** Gastro-esophageal reflux disease (GERD) still poses several clinical issues to be faced, from clinical and instrumental diagnosis to medical and surgical therapy. In this review we provide the most updated evidence on the management of GERD. Practice-oriented questions on GERD are answered through a concise review of current literature. The aim is to provide clinicians a practical tool to guide them through the management of patients with GERD.

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## INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a complex but common condition[1] that poses several issues to the clinicians. Prompt endoscopy should be reserved only to patients with symptoms of GERD and alarm features or multiple risk factors for Barrett's esophagus. Grade A esophagitis is not sufficient to diagnose GERD, and only patients with grade C and D esophagitis should undergo endoscopic follow-up after proton-pump inhibitors (PPIs). Evidence of posterior laryngitis is not reliable for diagnosing GERD. Reliable selection of patients with PPI-refractory GERD who can benefit from anti-reflux surgery is a critical issue and relies on careful evaluation including impedance-pH monitoring. Prokinetics may be used in patients with concomitant dyspeptic symptoms, whereas potassium-competitive acid blockers (P-CABs) may be an option for erosive esophagitis.

### QUESTION 1: SHOULD I PERFORM ENDOSCOPY IN ALL PATIENTS WITH GERD SYMPTOMS?

Answer: According to more recent international guidelines, a clinical response to an empiric 8-wk once-daily PPI therapy is diagnostic for GERD in patients with heartburn or acid regurgitation[2,3]. This pragmatic approach has a sensitivity of 78% and specificity of about 54%[4], which means to avoid unnecessary endoscopy in more than half of patients with symptoms of GERD. In fact, it should be emphasised that most patients with confirmed GERD do not present endoscopic findings of erosive esophagitis[2]. On the other hand, prompt endoscopy is recommended for patients with GERD symptoms and dysphagia or other alarm features (*e.g.*, weight loss, vomiting, or signs of gastrointestinal bleeding). Endoscopy is also recommended in all patients with GERD symptoms and at least 2 of the following risks factors for Barrett's esophagus: Age  $\geq$  50 years, male gender, Caucasian ethnicity, obesity, family history for Barrett's esophagus or esophageal adenocarcinoma, and smoking[2,5]. Indeed, the prevalence of Barrett's esophagus among patients with GERD symptoms is only about 5%-7%[6,7], therefore endoscopy should be reserved to patients with multiple risk factors for this condition.

### QUESTION 2: IS EROSIVE ESOPHAGITIS SPECIFIC FOR DIAGNOSIS OF GERD?

Answer: Traditionally, endoscopic erosive esophagitis is considered specific for the diagnosis of GERD. The Los Angeles (LA) classification is currently the most used one for grading erosive esophagitis and considers 4 degrees: Grade A and B, non-confluent erosions (*i.e.*, mucosal breaks) of longitudinal extension  $\leq$  5 mm or  $>$  5mm, respectively; grade C and D, confluent erosions between multiple folds affecting  $<$  75% or  $\geq$  75% of the circumference, respectively[8]. According to recent international guidelines, the presence of grade A erosive esophagitis is not sufficient to diagnose GERD, as it can be present in 5%-8% of healthy subjects who do not experience symptoms of GER nor present complications such as Barrett's esophagus, and can be linked to other factors such as drugs or infections[2,3]. Grade B esophagitis can be considered diagnostic of GERD in the presence of typical symptoms of GERD that respond to PPI therapy, while grade C and D esophagitis are always diagnostic for GERD [2]. Nevertheless, it should be noted that erosive esophagitis is mostly healed by PPI therapy, therefore PPIs should be stopped at least 2 wk before endoscopy[2].

### QUESTION 3: WHEN TO PERFORM ESOPHAGEAL BIOPSIES IN PATIENTS WITH GERD SYMPTOMS?

Answer: Esophageal biopsies are currently not considered in patients with GERD symptoms as they are of little value for the diagnosis of GERD. Histopathological findings that are variably associated with GERD, including dilation of the intercellular spaces and inflammatory intraepithelial cells and necrosis, have been described in the literature[9], but are flawed by a suboptimal specificity[10]. In fact, esophageal biopsies should be performed to diagnose eosinophilic esophagitis. This condition might coexist when patients refer also dysphagia and food bolus impaction in the esophagus. In this case, at least 6 biopsies should be performed in multiple esophageal sites[11]. Since PPIs can mask endoscopic and histological features of eosinophilic esophagitis, PPI therapy should be stopped at least 2 wk before endoscopy.

### QUESTION 4: SHOULD HIATAL HERNIA ALWAYS BE IDENTIFIED AND MEASURED?

Answer: The systematic identification and measurement of hiatal hernia is important for several reasons: (1) Hiatal hernia is a predisposing factor for GERD; (2) If present, it should be corrected during laparoscopic fundoplication when technically feasible; and (3) Measurement of hiatal hernia presupposes the correct identification of landmarks, *i.e.*, diaphragmatic hiatus and esophago-gastric and squamocolumnar junctions, in turn necessary for the correct diagnosis of Barrett's esophagus. Therefore, although some evidence suggests that endoscopy is not the test of choice for measuring hiatal hernia [12], it is important to standardise this procedure to maximise its accuracy and reliability. First, endoscopy must be performed under sedation to avoid retching that could temporarily displace the gastric fundus. Second, the measurement must be carried out between the diaphragmatic hiatus and the top of the gastric folds (*i.e.*, esophagus-gastric junction). Last, excessive insufflation should be avoided, and the measurement should be always carried out during the same phase of the examination, *i.e.*, during extubation in order to minimise the effect of gastric prolapse following intubation.

### QUESTION 5: SHOULD PATIENTS WITH EROSIVE ESOPHAGITIS UNDERGO REPEAT ENDOSCOPY AFTER TREATMENT?

Answer: The rationale for repeating endoscopy after treatment in patients with erosive esophagitis is mainly linked to the possibility that inflammation could obscure the visibility of an underlying Barrett's esophagus. Secondly, in those with more severe erosive esophagitis (LA grade C or D) it is advisable to check for the healing of the lesions and possible occurrence of complications (*e.g.*, peptic stricture) after adequate therapy with PPIs. Barrett's esophagus at repeat endoscopy after PPI treatment for erosive esophagitis has been reported in up to 12% of cases[13]. However, Barrett's esophagus is mostly obscured by LA grade C and D esophagitis, with a lower incidence reported in grades A and B[13]. Therefore, guidelines currently recommend repeating endoscopy after an 8-wk course of PPI therapy only in patients with LA grade C and D erosive esophagitis[14].

### QUESTION 6: IS AN INSTRUMENTAL FINDING OF LARYNGITIS A SPECIFIC SIGN OF GERD?

Answer: The extra-esophageal manifestations of GERD are various and their association with GERD cannot always be unequivocally proven. Some findings at laryngoscopy, such as erythema and oedema of the vocal cords or larynx, may be related to GERD, but the specificity of these signs for the diagnosis of GERD is as low as 40%[15]. These findings may be attributable to other conditions, such as post-nasal drip syndrome or exposure to allergens and other environmental irritants[15]. Furthermore, the response to PPI therapy in these patients is unreliable due to the large placebo effect. Therefore, the presence of laryngeal symptoms (*e.g.*, cough, hoarseness), even when associated with an instrumental finding of laryngeal inflammation, is not sufficient for the diagnosis of GERD, and patients should be referred for further diagnostic investigations to confirm this diagnosis, *e.g.*, endoscopy if not previously performed and/or impedance-pH monitoring[2].

## QUESTION 7: IS PH MONITORING ALONE INFERIOR TO IMPEDANCE-PH MONITORING TO DIAGNOSE GERD?

Answer: Ambulatory reflux monitoring, including pH-monitoring and impedance-pH monitoring, is the method of choice to confirm or exclude the diagnosis of GERD[2,3]. Impedance detects the movement of fluids and gas inside the esophagus independently from their acidity, thus distinguishing weakly acid from acid refluxes and reliably documenting the total number of reflux events throughout the recording period. Two additional applications need to be briefly mentioned: The post-reflux swallow-induced peristaltic waves (PSPW) index is the ratio between reflux episodes timely followed by a swallow event, and all the reflux episodes; this measure assesses esophageal chemical clearance due to the esophago-salivary reflex and has been shown to be impaired in GERD[16,17]. The mean nocturnal basal impedance (MNBI) is the mean baseline impedance value in three 10-min periods from the most distal impedance channel during nighttime recumbent period; this measure assesses the integrity of esophageal mucosa and is reduced by the chronic inflammation due to GERD[16,17].

Recent evidence has shown that pH monitoring alone, using esophageal acid exposure time (AET) > 6% according to the Lyon consensus[3] confirms the diagnosis of GERD only in 45% of patients with PPI-responsive heartburn[17]. On the other hand, impedance-pH monitoring with the evaluation of total refluxes, MNBI and PSPW index increases the diagnostic yield of about 20%, especially allowing to better characterise patients with inconclusive AET between 4% and 6%[17]. Of note, impedance-pH monitoring can identify ongoing reflux in a much higher proportion of PPI-refractory patients than pH monitoring alone, when performed on-therapy[18]. Therefore, impedance-pH monitoring should be considered the test of choice to confirm or rule out a diagnosis of GERD.

## QUESTION 8: HOW SHOULD I MANAGE PPI THERAPY BEFORE IMPEDANCE-PH MONITORING?

Answer: The choice of performing impedance-pH monitoring off-PPI or on-PPI depends on the clinical goal. Impedance-pH monitoring should be performed off-PPI to demonstrate that pathological gastro-esophageal reflux underlies symptoms in a patient with unproven GERD[3]: That is when, for instance, a patient with normal endoscopic findings complains of typical or extra-esophageal symptoms and requires continuous PPI for symptom control or asks for anti-reflux surgery. On the other hand, impedance-pH monitoring should be performed on-PPI to confirm or exclude that ongoing reflux is the cause of inadequate response to double-dosage PPI in a patient with documented GERD[3].

## QUESTION 9: WHEN SHOULD I VERIFY PATIENT ADHERENCE TO PPI THERAPY?

Answer: Modality and timing of PPI intake are key factors in obtaining an adequate response. Proton pump inhibitors should be taken at least 30 min before the first meal, preferably in the morning before breakfast, and in case of a second dose in the evening before dinner. This allows to achieve the maximum suppression of gastric acid secretion by inhibiting proton pumps before these are activated by food[19]. However, there is evidence that a large proportion of patients with unresponsive GERD symptoms do not take PPIs 30 min before the first meal[20]. Additionally, two studies found that only about half of patients correctly adhered to PPI therapy prescriptions for more than 80% of the time and that increasing compliance was typically related to symptom improvement[19]. Indeed, patient adherence to PPIs should be always verified in case of PPI-refractory symptoms.

## QUESTION 10: WHEN DO I REFER A PATIENT WITH PPI-REFRACTORY SYMPTOMS TO ANTI-REFLUX SURGERY?

Answer: Patients with symptoms suggestive of gastro-oesophageal reflux unresponsive to PPIs should first be investigated about compliance and adherence to therapy. In case of good compliance, they should be referred for off-PPI upper gastrointestinal endoscopy and impedance-pH monitoring to confirm GERD diagnosis. Indeed, PPI therapy is so effective for typical GERD symptoms when properly administered that true PPI-refractoriness should prompt to verify the actual correlation between symptoms and reflux. On the other hand, in case of proven GERD impedance-pH monitoring should be performed on double-dosage PPI therapy started from at least 8 wk, in order to reliably link PPI-refractory symptoms to ongoing reflux and exclude reflux-unrelated symptoms. Indeed, in a recent randomised controlled trial (RCT) evaluating 366 patients referred for PPI-refractory heartburn only 21% of cases showed a clear-cut impedance-pH correlation between heartburn and gastro-esophageal reflux[21]. This highlights the importance to refer for surgical fundoplication only patients with PPI-

refractory GERD confirmed by impedance-pH monitoring. Correct selection of patients is crucial to maximise the outcome of anti-reflux surgery, which can be as high as 90%[18].

### QUESTION 11: WHICH IS THE ROLE FOR PROKINETICS IN PATIENTS WITH GERD?

Answer: Dyspeptic symptoms can present in nearly half of patients with GERD, and the probability of dyspepsia in individuals with weekly GER symptoms is nearly 7-fold higher than in subjects without GERD[22]. There is a pathophysiological basis for this association, as prolonged postprandial gastric distention and increased basal intragastric pressure may lead to an increased gastro-esophageal pressure gradient, favoring reflux episodes. Therefore, prokinetics such as metoclopramide and domperidone may be beneficial when added to PPI therapy in patients with concomitant dyspeptic symptoms. However, the caveat is that their use can be limited by side effects including drowsiness, agitation, irritability, depression, dystonic reactions, and tardive dyskinesia for metoclopramide, whereas QT monitoring seems prudent for domperidone due to small risk for ventricular arrhythmia and sudden cardiac death[2].

### QUESTION 12: WHICH IS THE ROLE FOR P-CABS IN PATIENTS WITH GERD?

Answer: P-CABs competitively inhibit proton pumps and have been licensed in Japan for the treatment of GERD since 2015[19]. Differently from PPIs, vonoprazan can block both inactive and active proton pumps, resulting in a higher and longer-lasting suppression of gastric acid secretion[19]. Further, its elimination is independent from CYP2C19 metabolism, probably contributing to explain its greater effect[19]. A recent meta-analysis on 19 RCTs found that vonoprazan was superior to PPIs in healing erosive esophagitis, whereas there was no difference in the improvement of GERD symptoms[23]. However, evidence on refractory GERD is scarce, and more studies from Western countries are needed to expand knowledge on the effectiveness of this drug in the setting of erosive reflux disease.

## CONCLUSION

GERD is one of the most frequent gastroenterological conditions, yielding a considerable amount of resource consumption in health services[1]. Although several guidelines have been published[2,3], the management of patients with GER symptoms is still controversial. Currently, for example, there is no gold standard for diagnosing GERD, as diagnosis relies on a combination of symptoms, response to PPI therapy, endoscopy, and ambulatory reflux monitoring. Recent evidence-based recommendations provide new insights regarding erosive esophagitis and the management of patients refractory to PPIs [2,3]. This review provides the answers to questions which were selected after collegial discussion between the authors, also taking into account the most debated issues with general practitioners and non-dedicated gastroenterologists, that may help physicians in the management of patients with GERD (see Table 1). The answers are based on the overview of current guidelines and recommendations and on recent evidence provided from systematic reviews and clinical trials.

**Table 1 Practice-oriented answers to clinical questions on the management of gastro-esophageal reflux disease**

| No. | Question   | Answer  |
|-----|--|---|
| 1   | Should I perform endoscopy in all patients with GERD symptoms?                     | Endoscopy should be reserved for patients with GERD symptoms and either alarm features or multiple risk factors for Barrett's esophagus |
| 2   | Is erosive esophagitis specific for diagnosis of GERD?                             | Only LA grade C and D esophagitis are always specific for GERD  |
| 3   | When to perform esophageal biopsies in patients with GERD symptoms?                | Esophageal biopsies should be performed only when eosinophilic esophagitis is suspected   |
| 4   | Should hiatal hernia always be identified and measured?                            | Hiatal hernia should always be identified and measured  |
| 5   | Should patients with erosive esophagitis undergo repeat endoscopy after treatment? | Only patients with LA grade C and D esophagitis should undergo repeat endoscopy after PPI therapy                                       |
| 6   | Is an instrumental finding of laryngitis a specific sign of GERD?                  | Laryngoscopic findings of laryngitis are not specific signs of GERD   |
| 7   | Is pH monitoring alone inferior to impedance-pH                                    | Impedance-pH monitoring is the test of choice to confirm or rule out GERD   |

|    |  |   |
|----|--|---|
|    | monitoring to diagnose GERD?   |   |
| 8  | How should I manage PPI therapy before impedance-pH monitoring?                | The choice of performing impedance-pH monitoring off-PPI or on-PPI depends on the clinical goal                           |
| 9  | When should I verify patient adherence to PPI therapy?                         | Adherence to PPI therapy should be always verified in case of PPI-refractory symptoms                                     |
| 10 | When do I refer a patient with PPI-refractory symptoms to anti-reflux surgery? | Only patients with PPI-refractory GERD confirmed by impedance-pH monitoring should be referred to surgical fundoplication |
| 11 | Which is the role for prokinetics in patients with GERD?                       | Prokinetics may be used in patients with GERD and concomitant dyspeptic symptoms  |
| 12 | Which is the role for P-CABs in patients with GERD?                            | P-CABs are promising antisecretory drugs, however more evidence is needed   |

GERD: Gastro-esophageal reflux disease; PPI: Proton-pump inhibitor; LA: Los Angeles; P-CABs: Potassium-competitive acid blockers.

## FOOTNOTES

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**Country/Territory of origin:** Italy

**ORCID number:** Leonardo Frazzoni [0000-0001-7084-6157](https://orcid.org/0000-0001-7084-6157); Lorenzo Fuccio [0000-0001-8618-2447](https://orcid.org/0000-0001-8618-2447); Rocco Maurizio Zagari [0000-0001-9949-8619](https://orcid.org/0000-0001-9949-8619).

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