

# Refractory GERD

## Introduction

Gastroesophageal reflux disease (GERD) is a common condition with 44% of American surveyed reporting heartburn at least once per month and 20% reporting symptoms once per week [1]. However, despite major advances in our understanding of this disease, management of GERD is still a challenge. Proton pump inhibitors (PPIs) are more effective than H2 receptor antagonist (H2RA) in the initial healing of erosive esophagitis, symptom relief, and maintenance [2]. Due to its established efficacy and safety, PPI treatment is used as the initial “test” in diagnosing GERD in the absence of bleeding, anemia, weight loss, or dysphagia. A daily dose of PPI provides adequate symptom relief in most patients, however, dose escalation of twice a day may be needed in some.

Patients unresponsive to PPI therapy are often labeled as having “refractory GERD.” However, this term is poorly defined and has different meanings in different countries. In Europe, “refractory GERD” may be defined as a lack of response to once daily PPI therapy, while in the US, it is defined by lack of response to twice daily PPI therapy. More importantly, the cause of refractory GERD is poorly understood. It is estimated that 10% to 40% of patients with GERD failed to respond to once daily PPI therapy. Between 1997 and 2004, there has been nearly a 50% increase in the usage of at least twice daily PPI in patients with GERD [3]. These numbers have substantial health care cost implications.

The first step in the management of PPI-refractory patients is to confirm compliance and ensure that dosing and timing of medications are adequate. Delayed release PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) should be taken 30 minutes prior to meals. The more recent PPIs (dexlansoprazole) may not need to be taken prior to meals. It is shown that most patients are either not compliant with taking the medications or take them incorrectly, with respect to meal times. Thus, review of patient compliance and adherence to timing of PPI intake is essential. A randomized controlled trial in patients with persistent GERD symptoms despite a single daily dose of PPI, showed that increasing PPI to twice daily or switching to another PPI both resulted in symptomatic improvement in roughly 20% of patients without a clear advantage of either strategy [4].

The patients with persistent symptoms despite optimization of PPI therapy require further workup. Endoscopy is recommended for typical esophageal symptoms in order to look for erosive esophagitis (rare in acid suppressed patients) and exclude non-reflux esophageal disorders, such as eosinophilic esophagitis. If endoscopy is negative, as is most often the case, reflux monitoring is indicated. Objective quantification of reflux should be also considered in patients with extraesophageal symptoms that persist despite PPI optimization and in whom non-GERD etiologies have been ruled out through pulmonary, ENT, and allergy evaluation. Reflux monitoring will yield of 1 of 3 possible explanations for persistent symptoms despite therapy: (1) failure of acid suppression with ongoing symptomatic acid reflux, (2)

adequate acid control by ongoing symptomatic non-acid reflux, or (3) no acid reflux of any kind and/or no relationship between reflux and patients complaints (Table 1).

**Table 1:** Proposed etiologies for poor PPI response in a given patient initially suspected of having GERD.

Not GERD	Insufficient Acid Suppression
Rumination	Dosing
Aerophagia	Compliance
Motility disorder (achalasia)	ZE
Functional	PPI resistance
Delayed gastric emptying EoE (?)	
Weakly acid/non-acid	Hypersensitivity

Two key issues to consider when preparing to perform reflux monitoring are whether the test should be done while on PPI therapy or after cessation of this medication, and what tool to use (catheter based pH, wireless pH, or impedance-pH). Reflux monitoring off PPI (7 days after stopping therapy) can be performed with any of the available techniques (catheter or wireless pH or impedance-pH), because the main goal is to measure acid reflux. Reflux monitoring on PPI should be performed with impedance-pH monitoring to enable measurement of non-acid reflux. The yield of pH monitoring alone (without impedance) in a patient taking a PPI is very low because in acid suppressed patients reflux becomes predominantly non-acid. Data suggest that while on twice daily PPI therapy, the likelihood of continued esophageal acid exposure is less than 10% in typical GERD and only 1% percent in atypical GERD patients [5].

One approach (as to whether or not to perform these tests “off versus on” therapy) includes assessing the pretest probability likelihood of GERD. The patients with the low likelihood of GERD (complete absence of response to PPI, extraesophageal presentations without concomitant typical symptoms) may be tested off therapy. If the test is negative, GERD is excluded and other etiologies are pursued. The patients with a likelihood of GERD (at least partial response to PPI, typical symptoms, other

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features to suggest GERD such as a large hiatus hernia) may be tested while on therapy in search of reflux (acid or non-acid) that persists despite acid suppression [6]. In some patients, testing both off as well as on therapy is necessary in order to clarify the reason for PPI refractoriness. Finally, it is important to stress the importance of stopping PPI therapy with refractory symptoms in whom all testing is negative.

In most patients with continued symptoms despite PPIs, one must consider non-GERD causes such as gastroparesis, rumination, motility disorders, eosinophilic esophagitis, or functional disorders. Clinical setting will most likely determine if esophageal motility disorder such as achalasia should be in the differential diagnoses. This group of patients commonly present with not only regurgitation but also dysphagia to solids and liquids. Eosinophilic esophagitis should be considered and esophageal biopsies taken, especially in a young patient presenting with food impaction and/or dysphagia. Gastroparesis is often a missed diagnosis in many patients who have refractory GERD. This condition predisposes to GERD and GERD therapy alone will not result in complete symptom relief. Pro-motility agents and lifestyle modifications (including a low bulk/low-fat diet) as well as PPI therapy is in the main stay of therapy for gastroparesis.

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