Refractory gastro-oesophageal reflux disease: a major management issue in clinical practice

Refractory gastro-oesophageal reflux disease can be frustrating, for both patient and practitioner.

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Refractory oesophagitis (non-healing of erosions) is rare since the advent of potent gastric acid inhibition with proton pump inhibitors (PPIs). However, refractory gastro-oesophageal reflux disease (GORD) symptoms, both typical and atypical (cough, chronic hoarseness, asthma and atypical chest pain), have become a substantial clinical problem that is most prevalent in patients with non-erosive reflux disease.

The frequency and/or severity of GORD-related symptoms are likely to vary between patients, making it difficult to decide which symptomatic burden fulfills the definition of refractory GORD.

What defines GORD as refractory to treatment is controversial. Some clinicians believe that only patients with an incomplete response or lack of response to PPIs twice daily should be considered as PPI failures, while others regard a lack of symptomatic response to once-daily PPI as sufficient evidence. The frequency and/or severity of GORD-related symptoms are likely to vary between patients, making it difficult to decide which symptomatic burden fulfills the definition of refractory GORD. Therefore, a too restrictive definition of refractory GORD may exclude many true sufferers.[1]

Approximately 10 - 40% of GORD patients do not have a complete or even partial symptomatic response to a standard PPI dosage, hence the increasing practice of doubling the dose.[2] Furthermore, less than 50% of the GORD patients are satisfied with their medical treatment, and only 58% of those receiving a PPI report a satisfactory therapeutic response.[3]

Endoscopic healing and symptom relief are achieved within 8 weeks in the majority of patients with GORD.[4] However, patients with severe oesophagitis (e.g. Los Angeles grade C and D oesophagitis) may take longer to heal. Many of the possible causes for non-response are easy to address, but the timing and sequence of diagnostic testing, especially impedance pH studies, are more difficult and problematic.

Refractory GORD: possible causes of symptoms

Patients unresponsive to PPIs comprise a group who may require more aggressive therapy and another who need an underlying cause defined. Causes of persistent symptoms despite twice-daily PPI therapy include poor compliance and improper dosing of PPIs.

Inadequate PPI response

The efficacy of the PPIs is dose dependent and the healing of oesophagitis is proportional to the fraction of the day that the pH is above 4.[5] Nocturnal acid breakthrough, defined as intragastric pH<4 for more than an hour in the overnight period, is observed in up to 70% of normal subjects on PPIs taken twice daily and may be responsible for the majority of patients with refractory GORD.[6] Other factors that may also contribute include decreased bioavailability, variations in drug metabolism, acid hypersecretion and *Helicobacter pylori* status. The bioavailability of the different PPIs varies but does not normally lead to clinically relevant significant differences in acid suppression.[7] Although timing of PPI ingestion with respect to meals has little influence on absorption, it is generally recommended that these drugs should be taken 15 - 30 minutes before meals to reach peak serum levels prior to meal-stimulated acid secretion.[8] Genetically determined differences in PPI metabolism and, more specifically, rapid metabolism associated with mutation in the 2C19 isoform of cytochrome p450, may influence their efficacy. However, drug resistance is a rare condition and is presumably caused by mutations of the proton pump. The role, if any, of *Helicobacter pylori* in patients with refractory GORD on adequate PPI treatment still needs to be defined.

Other causes of symptoms

If a patient stays symptomatic despite adequate acid suppression, factors implicated in this include weakly acid reflux, duodenogastric/bile reflux, oesophageal hypersensitivity, concomitant functional

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bowel disease, psychological co-morbidities, delayed gastric emptying and eosinophilic oesophagitis.[9]

Weakly acidic GORD is the reflux of gastric contents with a pH between 4 and 7 into the oesophagus and may be associated with typical reflux symptoms as well as regurgitation and a sour or bitter taste in the mouth. In one study of patients who failed PPI therapy twice daily 31% had positive symptom index (SI) with weakly acidic reflux, 11% had acidic reflux, and 58% had a negative SI. Interestingly, atypical symptoms were least likely to be preceded by a weakly acidic reflux event.[10]

Duodenogastro-oesophageal reflux (DGOR) is the reflux of duodenal contents through the stomach and into the oesophagus. It has been shown in a recent study to be significantly more common (64%) than acid reflux (37%) in patients who continued to have GORD-related symptoms on either standard-dose or double-dose PPI treatment. Patients with erosive oesophagitis who did not respond to PPI treatment experienced a higher number of DGOR episodes (35 v. 15.5) and longer exposure time to DGOR (11.9% v. 6.3%) than non-erosive reflux patients in whom PPI therapy failed.[11]

The role of *visceral hypersensitivity* has not been specifically studied in patients who failed PPI treatment. However, most patients who do not respond to PPI therapy have non-oesophageal reflux disease (NORD) and up to 50% have functional heartburn. It is hypothesised that functional heartburn is composed of a heterogeneous group of patients of whom a significant subset is unlikely to have GORD as the underlying stimulus for their heartburn.[12] Furthermore, studies evaluating patients who did not respond to PPI treatment twice daily demonstrated that approximately 50 - 60% have negative SI between symptoms and any type of gastro-oesophageal reflux.

Delayed gastric emptying has been shown to contribute to the failure of PPI therapy in patients with GORD. Thus far, there are very few studies that have evaluated the frequency of gastric emptying in patients who did not respond to PPI therapy. Nevertheless, the rapidly growing number of patients with diabetes mellitus and those using narcotics for pain syndrome might soon make gastroparesis one of the leading causes of PPI failure.

Eosinophilic oesophagitis is relatively uncommon and unlikely to be responsible for a significant portion of patients who fail PPI treatment. The relationship between GORD and eosinophilic oesophagitis has not yet been fully explored. GORD-related symptoms only affect up to 43% of adults with eosinophilic oesophagitis, who in many instances present with dysphagia or have a history of food impaction. These are alarm symptoms necessitating urgent upper gastrointestinal endoscopy.

Lastly, in a recent review of the literature on GORD and *psychological co-morbidity* it was concluded that this is common among GORD patients and appears to afflict all GORD phenotypes. Sexual and physical abuse is also common in GORD patients. Stress enhances perception of oesophageal acid exposure. Treatment for GORD, especially in those who are not responsive to antireflux treatment, may require further evaluation for psychological co-morbidity. The role of psychological co-morbidity and emotional stress in PPI failure has been scarcely studied.[13]

Additional studies

Most of the available diagnostic approaches used in this challenging patient population group have limited clinical application and lack supportive evidence. Additional testing mostly requires referral to specialied centres.

All patients suspected of experiencing PPI failure should be assessed for compliance.

Repeat upper endoscopy

Patients who had a limited initial examination or severe erosive oesophagitis, may benefit from a repeat endoscopy. However, the presence of oesophageal erosions may be indicative of poor compliance. Biopsies of persistent ulcerative lesions are imperative to exclude oesophageal carcinoma. It may also be helpful to exclude other causes of oesophagitis such as infection or pill oesophagitis by repeat endoscopy.

Oesophageal pH monitoring

In patients with persistent typical GORD symptoms despite twice daily PPI therapy, standard transnasal oesophageal pH monitoring is most likely to be normal, but where adequate acid suppression is in question, a 24-hour pH study while taking medications can help to quantify the effectiveness of acid control.[14] The use of a wireless pH capsule to extend the period of pH recording to 48 hours failed to demonstrate additional diagnostic benefit and was technically associated with a high failure rate.[15]

Oesophageal impedance and pH monitoring (MII)

MII with pH sensor allows the detection of acidic (pH<4), weakly acidic (4≥pH<7), and weakly alkaline (pH≥7) reflux and can also determine the characteristics of the gastric refluxate (gas, liquid, mixed gas and liquid). Combined 24-hour pH impedance pH monitoring has demonstrated that persistent symptoms in patients on twice-daily PPIs may be related to non-acid reflux in a subset of patients as determined by either the symptom index or the symptom association probability.[16] The importance of proximal spread of the reflux column along with sensitisation of the oesophagus by prior reflux events as a cause of heartburn symptoms was highlighted in a recent publication.[17]

Oesophageal manometry

This is indicated in patients in whom a motility disorder is suspected. In addition, in patients with symptoms compatible with dyspepsia, irritable bowel syndrome or delayed gastric emptying, the appropriate diagnostic tests should be done.

Therapeutic approach

All patients suspected of experiencing PPI failure should be assessed for compliance. GORD is primarily a symptom-driven disease in which many patients continue to take medications as long as they experience symptoms.

Optimising therapy

This can be achieved by:

- Increasing the frequency of dosing and additionally taking a PPI before dinner to reduce nocturnal acid breakthrough. Patients should be reminded to take their medications 15 - 30 minutes before meals.
- A stepwise increase in the total PPI dose to achieve adequate acid suppression – even in patients who initially failed standard or relatively high-dose therapy.
- The addition of an H_2-receptor antagonist at night to suppress nocturnal acid breakthrough. It may be of theoretical benefit, but the effect may be short-lived as tolerance develops quickly, especially in patients who regularly take a night-time H_2-receptor antagonist.[18] Furthermore, the long-term efficacy of this approach is questionable as H_2-receptor antagonists are less effective than PPIs when used as maintenance treatment.
- Substituting one PPI for another. Very limited data are available on the effectiveness of this approach. However, in one controlled trial, switching patients with persistent heartburn on a standard-dose PPI to a different PPI was as effective as increasing the PPI dosage to twice daily for controlling heartburn symptoms.[19]

Lifestyle modifications

Lifestyle modifications (weight loss, smoking cessation, avoidance of large meals, etc.), may benefit individual patients, but this is yet to be proven.

Other therapeutic options

Baclofen, a gamma-aminobutyric acid ß-receptor agonist with inhibitory effect on transient lower oesophageal sphincter relaxation, has been shown to significantly reduce weakly acidic reflux and DGOR exposure as well as DGOR-related symptoms as compared with baseline. However, baclofen might result in a variety of side-effects such as confusion, dizziness, lightheadedness, drowsiness, weakness, and trembling.

The role of promotility drugs, pain modulators, bile acid binders and sucralfate is yet to be elucidated.

Surgery

Antireflux surgery should be considered in patients who require high doses of PPIs to control symptoms, particularly young patients who may require lifelong therapy.[20] Antireflux surgery has also been suggested to be effective in selected patients who failed PPI twice daily and have clear evidence of increased weakly acidic reflux when using MII. However, patients with continued symptoms despite adequate acid inhibition may not benefit from a surgical approach and this should rather serve as a warning that these symptoms may have a different aetiology.

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Conclusion

Refractory GORD is a complex clinical problem with especially GORD-related (both typical and atypical) symptoms that are becoming increasingly more resistant to PPIs. Optimising therapy is required before extensive testing with a rather limited yield is undertaken to define a possible underlying cause.

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In a nutshell

- Refractory oesophagitis (non-healing of erosions) is rare since the advent of potent gastric acid inhibition with proton pump inhibitors (PPIs).
- The frequency and/or severity of GORD-related symptoms are likely to vary between patients, making it difficult to decide which symptomatic burden fulfills the definition of refractory GORD.
- Endoscopic healing and symptom relief is achieved within 8 weeks in the majority of patients with GORD.
- Patients unresponsive to PPIs comprise a group who may require more aggressive therapy and another who need an underlying cause defined.
- Causes of persistent symptoms despite twice-daily PPI therapy include poor compliance and improper dosing of PPIs.
- The efficacy of the PPIs is dose dependent and the healing of oesophagitis is proportional to the fraction of the day that the pH is above 4.
- If a patient stays symptomatic despite adequate acid suppression, factors implicated in this include weakly acid reflux, duodenogastric/bile reflux, oesophageal hypersensitivity, concomitant functional bowel disease, psychological co-morbidities, delayed gastric emptying and eosinophilic oesophagitis.
- All patients suspected of experiencing PPI failure should be assessed for compliance.
- Lifestyle modifications (weight loss, smoking cessation, avoidance of large meals, etc.), may benefit individual patients, but this is yet to be proven.
- Antireflux surgery should be considered in patients who require high doses of PPIs to control symptoms, particularly young patients who may require lifelong therapy.

Single Suture

More girls than boys born in the tropics

Women living in tropical latitudes have a greater chance of giving birth to a girl, according to the first global study to link geographical latitude with the sex ratio of births. Normally, slightly more boys than girls are born.

Kristen Navara of the University of Georgia in Athens analysed birth data between 1997 and 2006 from 202 countries collected by the US Central Intelligence Agency. Navara's analysis of CIA data suggests that, worldwide, boys account for 51.3% of births, with just over 105 boys born for every 100 girls. But in tropical countries only 51.1% of births are boys. In the Central African Republic (CAR), only 49% of births were boys.

The differences are very small, but they translate into thousands of babies every year. In the CAR, for example, 1 400 fewer boys were born in 2006 than if the sex ratio had been 50:50. Other 'girl rich' tropical countries included Grenada, Mauritius and Bermuda. Apparently the results are similar to those from other studies of mammals, including meadow voles and Siberian hamsters, which have fewest males when the days are shortest. Navara thinks that the variation in the circadian hormone melatonin is a factor.

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