

Management of gastro-oesophageal reflux disease: role of proton pump inhibitor test and upper gastro-intestinal endoscopy

Il ruolo del PPI test e della esofago-gastro-duodenoscopia nella gestione della malattia da reflusso gastro-esofageo

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Summary

Authors report the available scientific evidence on the role of proton pump inhibitors and upper gastro-intestinal endoscopy in the management of patients with gastro-oesophageal reflux disease. Relative indications, advantages and pitfalls of various diagnostic and therapeutic strategies for cost-effective management of this condition are discussed. The most recent evidence-based guidelines are outlined.

Riassunto

Gli Autori riportano l'evidenza scientifica disponibile sul ruolo degli inibitori della pompa protonica e della esofago-gastro-duodenoscopia nella gestione dei pazienti affetti da malattia da reflusso gastroesofageo. Essi discutono le relative indicazioni, i vantaggi ed i limiti delle differenti strategie diagnostiche e terapeutiche e forniscono alcune linee guida comportamentali basate sulle più recenti prove di efficacia.

Definition of GERD

Gastro-oesophageal reflux disease (GERD) is one of the most common gastro-intestinal (GI) disorders, with typical symptoms of heartburn and acid regurgitation occurring weekly in about 20% of the general population¹⁻³. GERD should be diagnosed in all patients "who are at risk of physical complications from gastro-oesophageal reflux or whose well-being is appreciably impaired due to reflux-related symptoms"¹.

Management of GERD with typical symptoms

NON-EROSIVE REFLUX DISEASE

The presence of typical symptoms associated with endoscopic changes has a 97% specificity for the diagnosis of GERD^{2,3}. The intensity and frequency of GERD-induced symptoms have no consistent relationship to the severity of oesophagitis, i.e., symptoms are poor predictors of organic disease. In untreated patients with GERD, there is a low prevalence (< 10%) of severe oesophagitis and up to 70% of patients with typical symptoms of GERD have a

macroscopically normal mucosa (neither definite oesophageal mucosal breaks, nor Barrett's metaplasia) at upper GI endoscopy³. These patients suffer from non-erosive reflux disease (NERD), also referred to as endoscopy-negative reflux disease (ENRD). A negative endoscopy by no means excludes the possibility of GERD; it should actually strengthen the diagnosis of reflux disease by having excluded other mucosal disorders as a possible cause of symptoms.

NERD patients, who account for the vast majority of GERD patients, can be divided into 3 main groups on the basis of 24-hour pH monitoring: 1) those with abnormal acid exposure time; 2) patients with normal acid exposure time, but in whom symptoms and reflux events are significantly correlated (hypersensitive oesophagus); 3) patients with typical reflux symptoms but in whom all parameters of the pH study are normal⁴.

There is no gold standard for the diagnosis of NERD but a well-taken history is usually sufficient to confirm diagnosis and begin treatment. Endoscopy does not appear to be indispensable in this large group of patients. Thus, the more sensitive tool for the diagnosis of NERD is the proton pump-inhibitor (PPI) test. Most patients experience symptomatic improvement and, therefore, a short-term (4 weeks) of empir-

ic PPI therapy is a simple, safe and cost-effective diagnostic test⁵⁻⁷. This strategy can avoid further invasive diagnostic procedures with relevant cost savings (Table I).

In a recent evaluation of the clinical impact of performing an esophago-gastro-duodenoscopy (EGD) in the management of GERD, upper GI endoscopy improved the overall management in 40% of patients with alarm symptoms and 29% with persistent heartburn ($p = \text{NS}$). Medical treatment was changed in only 5% of patients, and no cancer was identified⁸. Early endoscopy should be performed in the presence of alarm symptoms, especially in males (dysphagia, odynophagia, weight loss, bleeding), when symptoms are refractory to initial treatment, in the pre-operative assessment and to provide reassurance when verbal reassurance is inadequate⁹.

In the absence of lesions in the oesophageal mucosa, the aims of NERD treatment are to: relieve symptoms, restore quality of life and maintain clinical remission. PPIs, in full doses, represent the treatment of choice for NERD patients, even if clinical trials show a lower efficacy in control of symptoms when compared to patients with erosive oesophagitis. Patients with NERD often require long-term therapy for symptom control. "On-demand" PPI therapy has been considered as the most cost-effective strategy for the long-term treatment of NERD¹⁰.

EROSIVE OESOPHAGITIS

Although with a limited diagnostic role, endoscopy is useful to: 1) clarify or confirm diagnosis; 2) assess severity of disease, providing guidance concerning the level of risk of oesophagitis; 3) define the best treatment strategies, providing a guide for the clinician in the choice of long-term management^{2,3,9}.

The results of endoscopy need to be reported in an explicit and clear language, using a standardised and validated system. Minimal mucosal changes

(erythema, oedema, friability) are of no use in the diagnosis of reflux oesophagitis since these signs are poorly reproducible. The Los Angeles classification of reflux oesophagitis is the most widely adopted and validated system for grading the severity of oesophagitis since it takes into account only consistently reproducible lesions, i.e., erosions or ulcerations (mucosal breaks). The LA score has 4 levels of severity (A-D) according to the radial extent of oesophageal mucosal breaks, independently of the presence of Barrett's oesophagus or other complications¹¹ (Table II).

The detection and grading of the severity of oesophagitis with the Los Angeles score is clinically relevant, since patients with more severe oesophagitis (grades C or D) are at greater risk of local complications, cannot afford PPI step down and often require anti-reflux surgery³.

Regarding the usefulness of follow-up endoscopy in reflux disease, evidence shows that repeat endoscopy is not usually indicated for the control of healing of oesophagitis. The absence of symptoms is a relatively sensitive indication of adequate control of oesophagitis. Symptom recurrence should be taken as an indication for the need of intensification of therapy rather than endoscopy^{2,3,9,12}. Follow-up endoscopy may be appropriate in patients with symptoms not responding to treatment, selected patients who had severe grades of oesophagitis or to perform further tissue sampling to clarify diagnosis (suspected Barrett's metaplasia masked by erosive oesophagitis).

Once identified, the optimal acute therapy should be maintained for at least 8 weeks. Depending on the initial treatment given, medical therapy is then adjusted in a step-down fashion to ascertain the least potent effective regimen. The need for maintenance therapy is determined by the rapidity of recurrence; recurrent symptoms in < 3 months suggest disease best managed with continuous therapy while remis-

Table I. Diagnostic tools in GERD.

Method	Comment
Typical symptoms	Heartburn and acid regurgitation are extremely specific for GERD
Empiric PPI therapy	Appropriate (together with lifestyle modifications) in patients with uncomplicated typical GERD; simple, safe and cost-effective; sufficiently sensitive and specific; failure to respond does not rule out disease
Endoscopy	Procedure of choice to detect complicated GERD; primary examination in patients with alarm symptoms or possible complications; negative findings do not rule out diagnosis
pH-monitoring	Best method for quantitative estimate of reflux; may confirm diagnosis in patients with normal endoscopy or with symptoms unresponsive to treatment; highly sensitive and specific for erosive oesophagitis
Oesophageal manometry	Useful only in pre-operative assessment to rule out achalasia

Table II. The Los Angeles Classification of Reflux Oesophagitis⁹.

Severity	Endoscopic appearance
Grade A	one or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
Grade B	one or more mucosal breaks > 5 mm none of which extends between the tops of the mucosal folds
Grade C	mucosal breaks that extend between the tops of two or more mucosal folds, but not circumferential (< 75% of circumference)
Grade D	mucosal breaks which involve at least 75% of the oesophageal circumference (circumferential)

sions of > 3 months can be adequately managed by repeated courses of acute therapy, as necessary. Patients who require continuous maintenance therapy should have an endoscopy to rule out Barrett's metaplasia and, in particular, dysplasia.

Role of endoscopy: detection of Barrett's oesophagus

Another primary indication for upper GI endoscopy in GERD is the identification of Barrett's oesophagus (BE), defined as the histologically confirmed presence of intestinal metaplasia in the oesophagus, a pre-malignant condition for the development of adeno-carcinoma¹³⁻¹⁶. Strong evidence supports the association of GERD and adeno-carcinoma of the oesophagus; however, the risk of cancer, in any given individual with GERD, is low (< 1% per year). Given the low absolute risk of cancer in GERD patients and the lack of demonstrated efficacy of endoscopic screening, insufficient evidence exists to endorse routine endoscopic screening of patients with chronic GERD symptoms. As for endoscopic and histological surveillance of patients with BE, some stronger indirect evidence does support this practice, performing circumferential four-quadrant jumbo biopsies every 1 or 2 cm of Barrett's extension¹⁵. Further research is necessary to clarify the effectiveness and cost-effectiveness of endoscopic surveillance in BE. Intervals of surveillance should be tailored individually according to the presence and grade of dysplasia¹⁶.

Management of GERD: extra-oesophageal and atypical manifestations

Extra-oesophageal manifestations of GERD are essentially complications of GERD that primarily involve organs that are in proximity to the oesophagus. Patients may present with symptoms involving the pulmonary system, chest pain and ear, nose, and throat (ENT) disorders¹⁷.

ENT manifestations of GERD have become more commonly recognized or suspected by physicians, although the direct association between symptoms and acid reflux has been difficult to establish. Possible mechanisms of GERD-mediated tracheo-pulmonary damage include direct-contact damage of mucosal surfaces by acid-pepsin exposure and a vagal reflex arc between the oesophagus and the upper aero-digestive tract, triggered by acid reflux¹⁸¹⁹ (see Chapter 1 by De Giorgi et al. in this Volume).

From the clinical standpoint, frequent heartburn is uncommon and lack of GERD symptoms is not unusual. Oesophageal mucosa injury is rarely present making upper endoscopy a low-yield procedure in both conditions. Nonetheless, endoscopic examination of the oesophagus is invariably scheduled in the diagnostic work-up by most of the other specialists involved in the care of the single patient. 24-hour dual-channel intra-oesophageal pH-metry may have greater diagnostic yields, but it is costly, invasive, and time-consuming. Pharyngeal acid exposure is more common in patients presumed to have extra-oesophageal reflux, but neither symptom scores nor video-laryngoscopic findings are predictive of pathological extra-oesophageal reflux as indicated by pH monitoring²⁰. Indeed, recent data do not support routine proximal oesophageal pH monitoring as a clinical tool in the evaluation of patients with suspected reflux-related ENT manifestations²¹. A trial of PPI treatment is increasingly being considered a first-line diagnostic test in those with suspected reflux-related extra-oesophageal symptoms. The duration as well as the dose of PPI should be based on the presenting symptoms, with patients having pulmonary manifestations often requiring twice-daily therapy for 2 to 3 months. PPI therapy can improve, to some extent, the laryngeal symptoms in laryngitis as well as asthma symptoms, asthma medication use, and lung function.

Non-cardiac chest pain (NCCP) is an atypical manifestation of GERD, because symptoms originate, in essence, from the oesophagus. In contrast with pulmonary or ENT manifestations, symptoms of reflux-

Table III. Guidelines on the use of PPI and endoscopy in GERD.

Clinical scenario	Recommendation
Typical symptoms, recent onset	No endoscopy, empiric therapy with PPIs
Atypical or extra-oesophageal symptoms	Empiric therapy with PPIs (double dose)
Alarm symptoms or signs	Endoscopy (\pm biopsy) as initial test
Long-standing GERD (> 10 yrs) or persistent or progressive symptoms	<ul style="list-style-type: none"> • Rule out other lesions • Determine severity of oesophagitis • Detect Barrett's oesophagus • Define best treatment strategy

related NCCP may be relieved with a 1-week, standard-dose treatment trial of anti-secretory therapy. The PPI test is a simple non-invasive, accurate and cost-saving test for evaluating patients with GERD-related NCCP. In two recent meta-analyses, the overall sensitivity and specificity for the PPI test were 80% and 74%, respectively, with a significantly high-

er discriminative power compared with 24-hr pH monitoring and endoscopy^{22,23}. Patients who fail to experience symptom resolution or improvement should undergo further diagnostic evaluations including 24-hour oesophageal pH studies while continuing their PPI therapy to establish persistent vs. absent acid reflux.

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