Overview: initial and long-term management of gastro-oesophageal reflux disease

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SUMMARY
Initial management of gastro-oesophageal reflux disease aims to confirm a symptom-based diagnosis, to relieve symptoms, to reassure the patient as to the treatable nature of reflux disease, and to initiate risk management and healing of oesophagitis. The aims of long-term management include adequate control of symptoms, prevention of complications, and improvement of quality of life. Management options in terms of use of proton pump inhibitors are either daily therapy (maintenance), intermittent courses of therapy (for example, 4 weeks, then cease and observe), or on-demand therapy. This overview discusses the advantages and disadvantages of these different strategies for the management of reflux disease.

INITIAL MANAGEMENT
Aims of initial treatment
The initial management of reflux disease has been greatly simplified by proton pump inhibitors, the first highly effective medical therapy for this condition.1, 2 The overall aim of initial management is to reach the phase of long-term care as quickly and as efficiently as possible. More specific aims are discussed below.

Diagnostic confirmation of reflux disease: This is important for both the patient and the doctor. Routine initial diagnosis depends primarily on the recognition of symptom patterns that suggest that they are caused by reflux. Fortunately, reflux-induced symptoms are quite distinctive in their patterning in a substantial majority of patients with reflux disease, as other diagnostic options are unsuitable for routine initial management – endoscopy being relatively insensitive and oesophageal pH-monitoring being impractical as a ‘front-line’ test.3 Both of these diagnostic tests are also relatively costly and frequently difficult to access promptly. As initial therapy is usually prescribed on the basis of symptom evaluation, relief of symptoms by therapy is the best possible confirmation of this diagnosis. Antacids and lifestyle/postural measures give poor symptom response rates;3 consequently, use of these as initial therapy will usually leave uncertainty as to whether the diagnosis was correct. H2-receptor antagonists (H2RAs) are a better option for diagnostic confirmation, but the substantially superior symptom response with proton pump inhibitor therapy gives the best chance of a crisp ‘first-shot’ confirmation of reflux disease by relief of symptoms.1–3 Such confirmation is economical, as it removes the need for repeated doctor visits and escalation of therapy (Figure 1). Compared with other proton pump inhibitors, esomeprazole has the most rapid and consistent symptom response; this superiority should enhance the utility of a trial of proton pump inhibitor therapy to confirm diagnosis.

Prompt symptom relief and patient reassurance: Prompt symptom relief is important to patients for two reasons. It is reassuring when prescribed therapy
gives a convincing benefit, but many patients with reflux disease also seek advice because they want relief from their reflux-induced symptoms. Proton pump inhibitor therapy best meets these needs and expectations.

Healing of oesophagitis: The need to achieve this aim during the phase of initial management has probably been overemphasized. For the 40% or so of patients who have oesophagitis, healing can probably be completed, if necessary, during long-term management. This should be achieved by appropriate, symptom-driven strategies discussed below, though data that formally assess these are limited.

Risk management: In the initial management phase, the major risk that needs to be guarded against is misdiagnosis. The initial symptom assessment should identify patients in whom early endoscopy should be performed in preference to a trial of empirical therapy. Endoscopy is indicated when the pattern of symptoms is nonspecific for reflux disease, or there are alarm features such as recent weight loss, dysphagia, anorexia or evidence of gastrointestinal bleeding.

What to do if initial treatment fails
Failure of a 4-week course of initial therapy should prompt a review of the symptom-based diagnosis, but this review should recognize that failure of response to true reflux disease is far more common than misdiagnosis when antacids, lifestyle/postural measures or H₂RAs are used as initial therapy.¹⁻³

When a review of symptoms confirms that these are typical for reflux disease, initial therapy should be intensified. If a proton pump inhibitor has not yet been used, this should be prescribed as it is by far the most effective intensification of therapy.

Once-daily morning dosing of a proton pump inhibitor is generally the most appropriate initial therapy, but in a relatively small minority of patients reflux-induced symptoms do not respond adequately to this. Much indirect evidence suggests that such failure arises from incomplete control of gastric pH in the second 12 h after proton pump inhibitor administration. Nocturnal reflux is less of a problem than previously believed in the full spectrum of patients with reflux disease, but in those who do not respond adequately to once-daily proton pump inhibitor therapy it is probably the most important cause of failure. Accordingly, proton pump inhibitor therapy should be intensified in these patients with the addition of a second daily dose, before the evening meal. Fewer patients are likely to need such escalation when they are treated with esomeprazole, but as yet experience on this is very limited.

Conclusions
Initial management should aim to confirm a symptom-based diagnosis, relieve troublesome symptoms, reassure the patient as to the benign and treatable nature of reflux disease, and initiate risk management and healing of oesophagitis when this is present.³ Best outcomes are achieved with these aims by the use of a proton pump inhibitor. The increment of efficacy of esomeprazole over other proton pump inhibitors further enhances the opportunities for achieving excellent results in this first phase of reflux disease management.

LONG-TERM MANAGEMENT
Aims and major options
The aims of long-term management include adequate control of symptoms, prevention of complications and improvement of quality of life.², ³ The clinician, when faced with formulating a long-term management plan for the patient with reflux disease, will have information on baseline symptoms and the response to initial therapy, but may or may not have the results of an endoscopic assessment. Assuming that the patient has required and responded appropriately to an initial trial
of acid-suppressive therapy with a proton pump inhibitor, which supports the clinical diagnosis of reflux disease, the medical treatment strategies available include:

- ceasing initial treatment and observing;
- immediately instituting continuous daily therapy;
- prescribing intermittent courses of therapy;
- recommending symptom-driven (on-demand) therapy.

The likely natural history of the disease, patient preference and cost-effectiveness should all influence the institution of an optimal management plan.

Disease severity and outcome

The likely natural history helps determine the long-term management. It is well established that, in both endoscopy-positive and endoscopy-negative patients, a significant proportion will relapse; between only 10% and 25% of patients will remain in remission after 6 months of stopping therapy. The relapse rate is driven in part by the underlying disease severity. Up to 90% of patients with erosive oesophagitis will relapse, but between 44% and 75% of patients with endoscopy-negative reflux disease will also relapse over 6 months. In addition, there is good evidence that patients with more severe oesophagitis (i.e. Los Angeles [LA] Grades C and D) are significantly more likely to relapse; although these form a minority of patients in the primary care setting, they represent a higher proportion in gastroenterology practice. In view of the higher risk of relapse, almost all patients with documented severe oesophagitis need long-term maintenance therapy. Hence, the results of endoscopy assist in making a decision. A potential surrogate marker of more severe oesophagitis in clinical practice in uninvestigated patients is the rapid failure to maintain remission after ceasing acute therapy, although its exact sensitivity and specificity are uncertain.

Based on maintenance trial data, approximately 20–30% of patients will have prolonged remission off all medication; these patients should, if possible, be identified in order to avoid the prescription of unnecessary medical therapy. This knowledge has led to consensus groups advocating a trial off therapy in all patients with uninvestigated symptomatic reflux disease treated with initial gastric acid suppression; if symptoms recur, a long-term management strategy will usually be needed.

Choice of medication based on efficacy

Once a patient has successfully responded to initial acid-suppressive therapy but relapsed off treatment, what long-term drug treatment should be considered? Proton pump inhibitors are more effective than H2RAs in the maintenance treatment of reflux disease. Howden et al. randomized patients with reflux disease to one of four management strategies, namely an H2RA or a proton pump inhibitor continuously, or step-up (from an H2RA to proton pump inhibitor) or step-down therapy (i.e. the reverse). The most efficacious strategy was maintenance proton pump inhibitor therapy. Other data suggest that using a maintenance treatment that is less potent than the agent used for healing typically results in high failure rates. The failure of H2RAs in long-term management may be related in part to inadequate suppression of meal-stimulated gastric acid secretion, as well as the development of tolerance. Doubling the dose of the H2RA does not appear to be an efficacious strategy. Cisapride is no longer recommended for reflux disease because of side-effects, and it had an efficacy equivalent to H2RA therapy.

Based on efficacy and safety, the ranking of medical treatments currently is:

1. twice-daily proton pump inhibitor;
2. standard-dose proton pump inhibitor;
3. standard-dose H2RA.

There is notably a large jump in terms of efficacy from H2RAs to proton pump inhibitor therapy, supporting the view that proton pump inhibitors should be used first line in long-term management.

A potential issue with the prescription of maintenance proton pump inhibitor therapy is the need for dose escalation over time. With the first-generation proton pump inhibitors, clinicians found that twice-daily therapy was required to control symptoms completely in up to 20% of cases initially. However, the available evidence of a need for dose escalation over time is limited. In a study of 230 patients with oesophagitis treated with omeprazole and followed up for 11.2 years, the initial dosage needs varied; however, following calibration to the minimally effective maintenance dose in the first year, few then required an increase in the dose over the follow-up period.
Choice of medication based on safety

Both H2RAs and proton pump inhibitors have remarkably good safety profiles. One issue that has been raised in relation to maintenance proton pump inhibitor therapy has been the association between progression of gastritis to atrophic gastritis and continued potent gastric acid suppression. This is a theoretical concern because of the potential risk of an increased incidence of gastric adenocarcinoma. Current data suggest that overall there is an increased risk of progression to atrophic gastritis and intestinal metaplasia (the cancer phenotype) in the presence of *Helicobacter pylori* infection, and the risk may be increased further with acid suppression.7,8 The most recent Maastricht consensus conference has recommended that if a patient has *H. pylori* infection and maintenance proton pump inhibitor therapy is planned, the infection should if possible be eradicated first to avoid a risk of progression of the gastritis.8

Choice of strategy

The management options in terms of use of proton pump inhibitors are either daily therapy (maintenance), intermittent courses of therapy (e.g. 4 weeks) then cease and observe, weekend therapy only, or on-demand therapy. Weekend therapy is not a successful strategy and cannot be recommended.3 In endoscopy-negative reflux disease, daily low-dose proton pump inhibitor therapy (e.g. omeprazole, 10 mg) has been shown to achieve good remission rates (73% in one study), but is more likely to fail in patients with oesophagitis.9

There is increasing support for the on-demand approach as the preferred strategy.10–12 For example, Bardhan *et al.* prospectively enrolled 526 patients and treated them with either an H2RA or proton pump inhibitor taken as needed.10 Approximately 50% of the patients did not need to take any acid-suppressive medication for a minimum of 6 of the 12 months of the study. The outcomes were similar whether or not patients had low-grade oesophagitis. Hence, on-demand acid-suppressive therapy appears to be a logical strategic approach. Moreover, this is often how patients take prescribed maintenance therapy. In other trials, on-demand therapy with omeprazole, 10 or 20 mg once daily, has shown remission rates of 69% and 83%, respectively.11 After 6 months of treatment with esomeprazole, 20 mg once daily on demand, 85% of patients were willing to continue the active drug, compared with about 48% of patients taking placebo.12

In patients with LA Grades A and B oesophagitis, data are lacking on the efficacy and safety of on-demand therapy. The consensus meetings have been unable to clarify the optimal approach in this group because of the lack of data. However, it is reasonable to suppose that minimal oesophagitis poses little or no risk of complications, and hence can probably be managed in the same fashion as endoscopy-negative reflux disease. Clinical trials are in progress to test this assumption. In contrast, patients with LA Grades C and D oesophagitis almost always require maintenance therapy, and this has been the management strategy recommended at consensus conferences.3

Choice of cost vs. effectiveness

Cost-effectiveness partly drives the decision of the preferred therapy. O’Connor *et al.* recently reviewed the cost-effectiveness of medical therapies for gastro-oesophageal reflux disease; they concluded that the most effective therapy was likely to be the most cost-effective one, although this was also driven by initial drug costs.13 Clearly, if two therapies are essentially of equal effectiveness but have different costs, then the least expensive would be the more appropriate option.

Choice of medication based on disease risk

The aims of therapy must also be driven by the available evidence of the risks. Hence, the effects of therapy need to be weighed against the long-term outcomes. There is some evidence, albeit limited, that, at least up to 15 years, patients with endoscopy-negative reflux disease usually do not progress to oesophagitis, and in this group of patients the issue remains primarily adequate symptom control.14 The situation is different in patients with more severe grades of oesophagitis, who most agree are at increased risk of complications; in these patients, healing of oesophagitis is relevant, as is the maintenance of this healing. Unfortunately, there remains a lack of adequate data on the risks of long-term oesophagitis, particularly with the milder grades.

Long-term management recommendations

Unless cost overwhelms the cost-effectiveness equation, proton pump inhibitor therapy represents the optimum
medical approach long-term. There is some evidence that the most effective therapy is preferable, but this is influenced by cost issues. In patients with uninvestigated reflux disease, on-demand therapy is now the choice. If this fails, endoscopy should be considered if not previously performed, to help guide further management, although patients in whom on-demand therapy fails will usually respond to daily therapy. Anti-reflux surgery is an alternative, but patient preference and the availability of a skilled surgeon as well as long-term costs will influence this.

What to do if long-term management fails

There are a number of possible reasons for failure of maintenance acid suppression in patients with reflux disease, in whom, despite instituting daily proton pump inhibitor therapy, symptoms persist or are poorly controlled. An incorrect diagnosis is particularly important to consider, but this is unlikely if the patient responded appropriately to initial acid-suppressive therapy. Pill-induced injury (e.g. from the bisphosphonates) can mimic reflux oesophagitis and should be eliminated. Inadequate compliance with therapy is another reason for treatment failure. Rare conditions such as Zollinger-Ellison syndrome causing acid hypersecretion or gastritis may need to be ruled out in patients with symptoms that are particularly difficult to control. There is also a sub-group of patients with more severe oesophagitis in whom gastric acid may be inadequately suppressed by standard or even double doses of proton pump inhibitors; these patients require higher-dose regimens to maintain reduced acid secretion. Nocturnal acid breakthrough does occur in a subset of patients, anti-refluxoesophagitis in whom gastric acid may be inadequately suppressed by standard or even double doses of proton pump inhibitors. H2RAs, whilst initially effective in reducing nocturnal acid, typically are subject to the development of tolerance. An alternative approach is to prescribe an H2RA on an as-needed basis before bedtime, to assist with night-time symptomatology.

REFERENCES


