

## DYSPEPSIA MANAGEMENT

# Management of reflux disease

J Dent

Gut 2002;50(Suppl IV):iv67-iv71

The management of reflux disease can be divided into three major phases, the first being diagnosis and severity assessment, the second, prompt initial control of symptoms, and the third, selection of a long term management approach that is tailored to meet individual patient needs and preferences. Throughout these phases of management, the major priorities should include achieving patient satisfaction and minimising management costs.

### SUMMARY

The management of reflux disease can be divided into three major phases: initial diagnosis/severity assessment, subsequent symptom control with diagnostic confirmation, and finally, a long term care plan tailored to individual patient characteristics. The now substantial experience from clinical studies in the full spectrum of patients with reflux disease underlines the primary importance of symptom assessment for diagnosis as the majority of patients have a distinctive symptom pattern. Endoscopy is a poor substitute for symptom assessment as in approximately 60% of reflux disease patients clearcut oesophagitis is absent. Symptom control, and thus diagnostic confirmation, is achieved most reliably with proton pump inhibitor (PPI) therapy so that initial therapy with one of these agents is an attractive option compared with initial therapy with less predictably effective agents. Long term care needs to provide effective medical or surgical control of reflux disease. In endoscopy negative patients, or those with only mild oesophagitis, intermittent courses of therapy or day to day symptom driven use of medication as needed, frequently succeed, with substantial reduction of the costs of medication. The choice between antireflux surgery and medical therapy in patients whose disease requires daily medication should be governed by informed patient preference and the quality of antireflux surgery available.

### INTRODUCTION

As gastro-oesophageal reflux disease is such a common condition, its appropriate management is important, particularly for primary care physicians. Decision making in the management of this condition is relatively complex because its diagnosis is not always straightforward, it has a very wide range of severity, the management of complications of oesophagitis is controversial, and several treatments are available that have varying levels of efficacy and safety. Major advances have been made in recent years in the

understanding of the pathogenesis<sup>1</sup> and diagnosis and treatment of this disorder.<sup>2</sup> There is now considerable interest in distilling clinical strategies in the light of these new understandings and capabilities. The outcomes of two recent workshops into clinical strategies for the management of reflux disease have been published recently.<sup>2,3</sup> These publications are a useful resource for a more detailed consideration of strategies discussed in this article.

Separation of patients with suspected reflux disease from those with dyspepsia is a fundamental strategy as this directs the majority of sufferers who have upper abdominal/retrosternal symptoms into one of two distinctly different management pathways. This is appropriate, given that the management needs of reflux disease patients differ very substantially from most patients with dyspepsia.

This article reviews the best management of reflux disease by dividing it into three phases, the first being diagnosis and severity assessment, the second, prompt initial control of symptoms, and the third, selection of a long term management approach that is tailored to meet individual patient needs and preferences. Throughout these phases of management, the major priorities of achieving patient satisfaction and minimising management costs need to be kept in mind.

### DIAGNOSIS AND SEVERITY ASSESSMENT

Contrary to commonly held beliefs, symptom evaluation is the most important assessment for this initial phase of management, and the results of any other investigations need to be interpreted in the light of the symptom evaluation.

#### Symptom evaluation

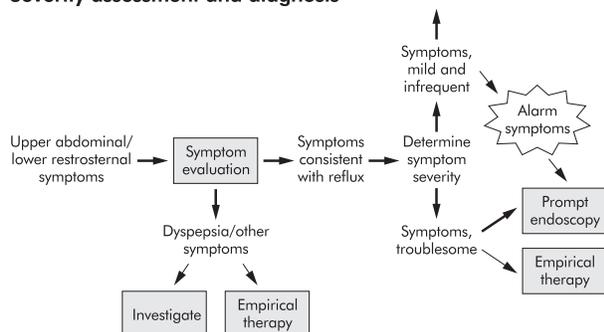
Symptom evaluation is used for three main purposes in this phase of the management of reflux disease—diagnosis, recognition of alert or alarm symptoms, and assessment of severity.

Symptom pattern evaluation is the single most important diagnostic step, as symptom patterning, particularly that of heartburn and its timing and precipitants, is usually characteristic in reflux disease. Despite this, there is a remarkable paucity of authoritative research into the sensitivity and specificity of particular symptom patterns for the diagnosis of reflux disease.<sup>2</sup> In addition, there has been little research into the formalisation of the structure and content of symptom evaluation to maximise its diagnostic value. Given the significant limitations of other diagnostic methods in

Correspondence to:  
Professor J Dent,  
Department of  
Gastrointestinal Medicine,  
Level 7, North Wing, Royal  
Adelaide Hospital, North  
Terrace, Adelaide  
SA5000, Australia;  
jdent@mail.rah.sa.gov.au

**Abbreviations:** H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; PPI, proton pump inhibitor.

### Severity assessment and diagnosis



**Figure 1** Schema for the initial management of patients with typical reflux induced symptoms. Adapted from Dent and colleagues,<sup>2</sup> with permission.

reflux disease (see below), there is a need for more research into symptom evaluation. As reflux disease symptoms are usually long standing, their duration is diagnostically helpful. If the duration of symptoms is short (for example, less than three months), this is atypical and should prompt the clinician to consider early endoscopy as an option if the severity of the symptoms warrants this.

The initial symptom assessment should include screening for alert symptoms (fig 1) that suggest the presence, and usually coexistence, of another serious problem, such as chronic peptic ulcer or oesophageal or gastric cancer, or of stricture or bleeding secondary to oesophagitis. If alert symptoms are present, it is generally agreed that prompt endoscopy is strongly indicated, a strategy that has been supported by a recent study.<sup>4</sup>

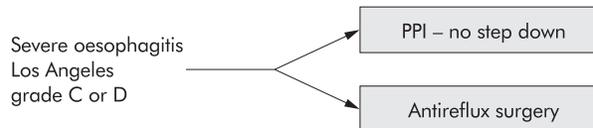
Assessment of the severity of symptoms is the third main application of symptom evaluation during initial management (fig 1). This is the most relevant measure of severity for the majority of people with reflux induced symptoms, and important for the choice of initial therapy, the next step in management. Heartburn and other reflux induced symptoms occur at least once a month in a substantial minority of the general population but in most, this is at such a low frequency and intensity that the symptoms have minimal impact on quality of life. People who experience reflux induced symptoms need to be separated into those who have reflux disease and those who do not. This important practicality was recognised by the following definition of reflux disease, which was discussed at the Genval workshop and supported by the majority of participants<sup>2</sup>: “The term ‘gastro-oesophageal reflux disease’ should be used to include all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms”. Adequate definition of the intensity and frequency of reflux induced symptoms enables the clinician to judge the impact of these on lifestyle, and so the nature of further action can be based on this severity assessment (see below). Formal evaluations of quality of life with validated instruments support the view that quality of life is impaired in proportion to the severity and intensity of reflux induced symptoms once a threshold has been reached. Precise definition of this threshold is not possible but heartburn probably needs to be present at least once or twice a week on a regular basis.<sup>2</sup>

### Endoscopic diagnosis

Endoscopy is useful in the initial phase of management for both diagnosis and severity assessment, and recognition of other important upper gastrointestinal mucosal disorders.

Unrealistic expectations of the diagnostic value of endoscopy for reflux disease have inappropriately devalued the symptom

### Summary — Los Angeles grade C or D oesophagitis 5–10% of patients



**Figure 2** Simplified schema for the management of patients with Los Angeles grade C or D (severe) oesophagitis. PPI, proton pump inhibitor.

assessment. Not unreasonably, it has been assumed that if reflux induced symptoms are troublesome, there will be endoscopically visible oesophagitis. There is now a wealth of data which show that this is simply not the case as substantially less than half of patients with troublesome reflux induced symptoms have clearcut reflux oesophagitis, defined as endoscopically visible and unequivocal breakage of the mucosal surface.<sup>5,6</sup> Neither the diagnostic sensitivity nor the specificity of endoscopy are improved by use of so-called “minimal mucosal changes” of the oesophageal mucosa, which fall short of mucosal breakage, as these changes cannot be recognised reliably by endoscopists, at least with currently available endoscopes.<sup>7</sup> It follows therefore that when endoscopy is negative in a patient who has a symptom based diagnosis of reflux disease, this diagnosis should not be discarded. Rather, if review of the symptoms confirms the impression that these are reflux induced, a normal endoscopy should actually strengthen the diagnosis of reflux disease by having excluded other mucosal disorders as a possible cause of the symptoms.

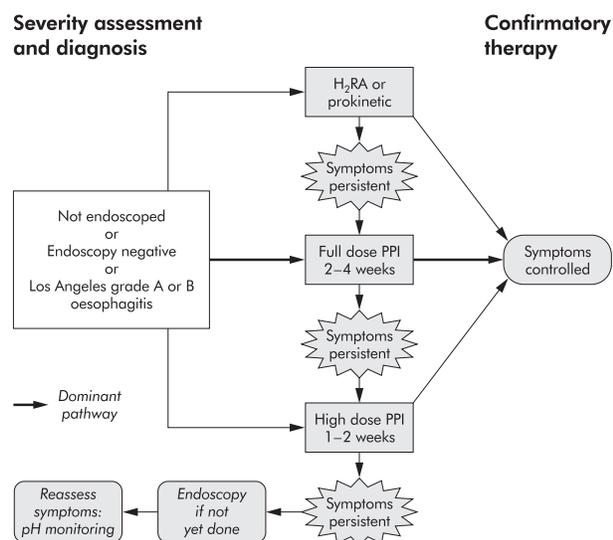
Endoscopy adds another dimension to the initial assessment of severity by detection and grading of oesophagitis. This is clinically relevant as indirect data indicate, unsurprisingly, that patients with more severe oesophagitis (Los Angeles grade C or D) are at greater risk of local complications from oesophagitis than in whom it is either mild or absent. Also, severe oesophagitis can usually only be healed and kept healed with PPI therapy.<sup>8</sup> Recognition that severe oesophagitis has these adverse features led the Genval workshop to put forward a specific management plan for patients with Los Angeles grade C or D oesophagitis (see below and fig 2). Importantly, endoscopic findings cannot be used as a surrogate for determining symptom severity by talking to the patient, as somewhat counterintuitively symptom severity has no consistent relationship to the severity of oesophagitis.<sup>2,9</sup>

### Role of pH monitoring in initial management

Oesophageal pH monitoring has become fairly widely available in recent years. This is not an appropriate initial diagnostic method for the typical patient because in most the diagnosis of reflux disease can be reached with a high level of accuracy without pH monitoring. This specialised investigation should also be used sparingly as it is a relatively expensive, inconvenient, and uncomfortable test. Oesophageal pH monitoring has its place further down the management pathway for the assessment of the minority of patients whose symptoms are atypical and/or poorly responsive to an adequate trial of therapy.<sup>2</sup>

### MANAGEMENT OF MILD REFLUX INDUCED SYMPTOMS

Patients with mild reflux induced symptoms that are not severe enough to satisfy the definition of reflux disease (see above) may seek advice on symptoms because of concerns regarding serious disease, or such symptoms may come to light during a general health screen. There is a remarkable lack of information on how many of these patients have oesophagitis and how they are best managed. On general



**Figure 3** Initial management plan for patients other than those known to have severe oesophagitis. Adapted from Dent and colleagues,<sup>2</sup> with permission. H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; PPI, proton pump inhibitor.

principles, reassurance that the symptoms are common and explained by “a touch of reflux” should be given. In some, adequate reassurance may require endoscopy. It seems reasonable to use a “step up” approach in those with this level of symptoms by first offering antacids for symptom relief and, if acceptable to the patient, modification of food intake patterns that are associated with symptom provocation. Other lifestyle measures such as weight loss, cessation of smoking, and bed head elevation are frequently advocated but there is no clear evidence that such measures are helpful, if they can be achieved.<sup>2</sup>

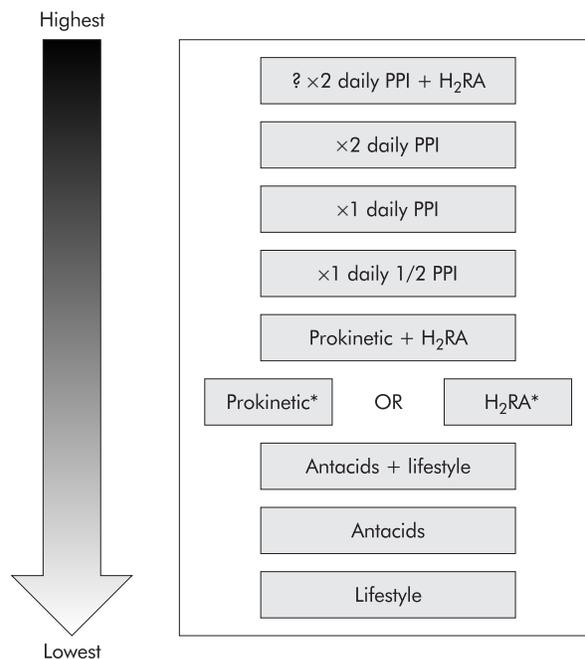
### INITIAL TREATMENT OF REFLUX DISEASE

From this point, this article deals solely with patients whose symptom intensity or frequency is sufficient for them to be defined as having reflux disease (see above and fig 1). It is useful to distinguish between initial and subsequent management of reflux disease as the priorities and strategies differ in these two settings (figs 2, 3).

#### Step up or high level initial therapy?

The traditional approach has been to initiate treatment of reflux disease with lifestyle measures and antacids and, if this fails, to increase the intensity of therapy progressively until there is an adequate response. The logic of such an approach is now highly questionable given the very superior and prompt response of reflux disease to short term PPI therapy.<sup>2-8</sup> By comparison, other therapies are much less effective and so their use is less likely to satisfy the prime aims of initial therapy—prompt relief of symptoms and, with this, confirmation of the diagnosis and reassurance of the patient. A critical evaluation of the available information on the efficacy of antacids and lifestyle measures led the Genval workshop to reject these for primary initial therapy in all patients with reflux disease, regardless of the presence or absence of oesophagitis.<sup>2</sup>

Minimisation of drug cost would seem to be the only logic for not using a PPI as initial therapy for reflux disease, but this logic is flawed as it fails to take into account the increased cost of other direct inputs to management such as physician time associated with treatment failure, let alone the indirect costs borne by the patient and community. Several studies performed in different management settings have concluded that the direct costs of initial PPI therapy are lower than those of initial therapy



**Figure 4** Mainstream options for the step down of daily long term medical therapy. H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; PPI, proton pump inhibitor. \*No clear dose-response established.

with H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs), by virtue of achievement of more prompt symptom relief in a single step.<sup>2 10 11</sup>

#### Escalation of intensity of therapy

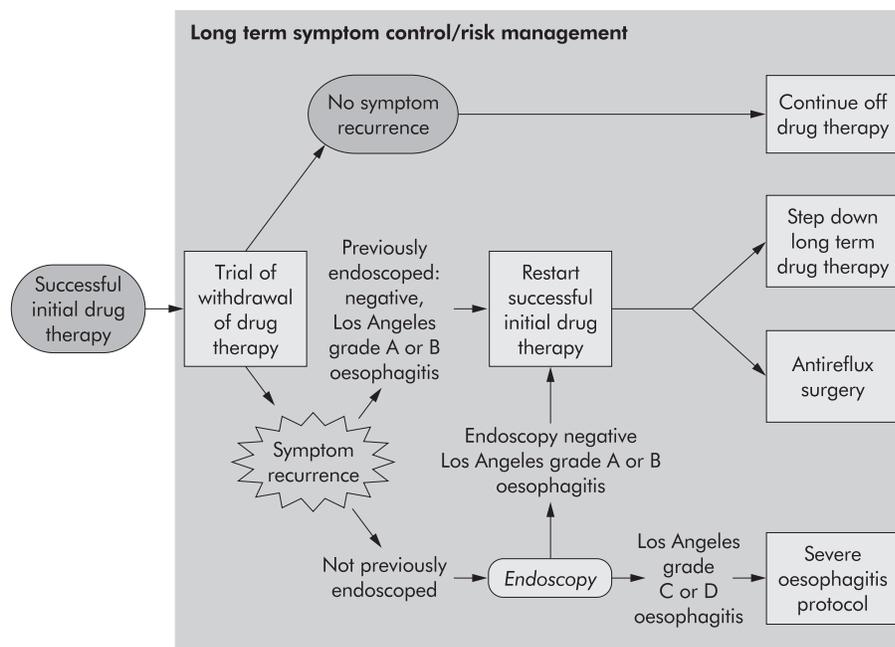
When initial therapy fails to control symptoms, either the diagnosis is incorrect or the chosen treatment has not been sufficiently effective. If on review of the patient it is concluded that reflux disease is still the most likely diagnosis, treatment needs to be intensified. The hierarchy of efficacy is now well defined and essentially the same for all patients with reflux disease, for both initial and long term management. The major steps are illustrated in fig 4. It can be seen from this that combination therapy with a H<sub>2</sub>RA and cisapride is not included as an option for intensification of therapy after treatment with one of these agents. This is on the grounds that monotherapy with a PPI is probably more effective than a combination of H<sub>2</sub>RA and cisapride. Data that compare these two treatments are however lacking.<sup>2 12</sup>

In the majority of patients with reflux disease, once daily PPI at standard dosages (for example, omeprazole 20 mg each morning) is effective but in a minority, double dose PPI is required. When given each morning, double dose PPI provides a useful increment of efficacy<sup>13</sup> but most benefit appears to be gained from giving the extra PPI separately before the evening meal.<sup>2</sup>

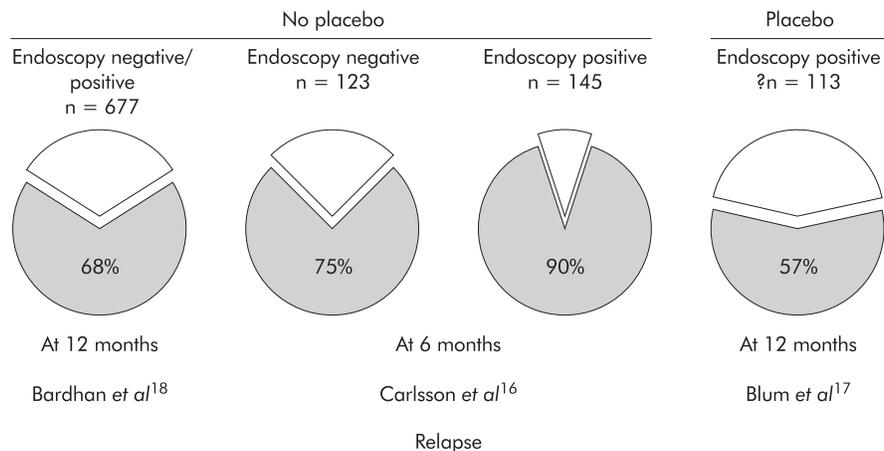
There are few data on escalation of the intensity of therapy beyond twice daily PPI. Further increase of the PPI dosage has been found to benefit some particularly refractory patients.<sup>14</sup> A combination of PPI and H<sub>2</sub>RA has been proposed as a further escalation of efficacy.<sup>15</sup>

### LONG TERM MEDICAL AND SURGICAL MANAGEMENT

The management plan should acknowledge that gastro-oesophageal reflux disease is predominantly a chronic relapsing disorder. Consequently, strategies need to be distilled for long term care after achievement of initial control of reflux disease. The balance of priorities for long term care differs from that of initial therapy. Adequate control of symptoms and any risk of reflux disease remains the major aim but



**Figure 5** Management pathways subsequent to initial management (see fig 3) in patients other than those known to have severe oesophagitis. Adapted from Dent and colleagues,<sup>2</sup> with permission.



**Figure 6** Variations in the rate of relapse from three different studies in untreated or placebo treated patients over six or 12 months, after withdrawal of successful initial acid suppression therapy. Data from Carlsson and colleagues,<sup>16</sup> Blum and colleagues,<sup>17</sup> and Bardhan and colleagues.<sup>18</sup>

minimisation of drug cost becomes a high priority as with an appropriate management plan this becomes the major determinant of the cost of care. An appropriate management plan seeks to minimise the frequency of visits to the doctor and to use endoscopy only when this is critical for risk management. The options of withdrawal of successful initial therapy, its continuation unchanged, step down therapy, or antireflux surgery are all appropriate, the choice being determined by individual patient characteristics.

#### Withdrawal and restart of successful initial treatment if necessary

It is only appropriate to withdraw successful initial therapy (fig 5) if this is followed by a useful period of untreated remission. In the case of patients known to have Los Angeles grade C or D oesophagitis, the possibility of such a remission is so small that a trial of withdrawal of therapy is not recommended (fig 2).<sup>2</sup> Freedom from relapse has been noted for periods of 6–12 months in a minority of patients with milder oesophagitis, or endoscopy negative reflux disease following withdrawal of 4–8 weeks of therapy (fig 5).<sup>2 16–18</sup> The

proportion of patients in remission 6–12 months after withdrawal of therapy varies considerably among studies (fig 6) but probably sufficient patients remain in remission to justify a trial of withdrawal of treatment in all but those known to have severe oesophagitis (fig 2).<sup>2</sup>

#### Continuation of long term therapy unchanged from initial successful therapy

This is the recommended strategy for medical therapy of patients with Los Angeles grade C or D oesophagitis for the reasons given above. Given the lower likelihood of relapse in endoscopy negative patients and those with Los Angeles grade A or B oesophagitis, tailoring of the intensity of medical therapy (fig 4) to the individual patient's response is reasonable in the interests of minimisation of drug cost. Strategies for this are discussed below.

#### Step down medical therapy

There are two major options for treatment step down—reduction of the intensity of daily therapy (fig 4) or intermittent use of therapy.

Several recent clinical trials have investigated the intermittent use of therapy. Compared with daily use of medication, this probably approximates more closely how most patients use medication for reflux disease. Both the use of courses of continuous therapy or dosing on a day by day basis according to symptom status (on demand therapy) have been shown to be effective and acceptable to patients, and to result overall in at least a halving of the amount of medication consumed compared with continuous therapy.<sup>18, 19</sup> A comparison between ranitidine and omeprazole has shown that PPIs retain their substantial superiority over H<sub>2</sub>RA when used in this way.<sup>18</sup>

Reduction of the intensity of daily therapy by stepping down the dose or therapeutic agent (fig 4) is a more traditional approach that is only logical if it leads to a reduction in medication cost. Whether this is achieved depends on the pricing structure of medications in a particular practice setting.

### Antireflux surgery

Discussion is always lively among doctors when the relative merits of long term medical therapy and antireflux surgery are being considered. The most important person to involve in such a discussion is the patient who ultimately must evaluate the best balance of trade offs associated with either surgical or medical therapy once he or she has been fully informed. A very important randomised comparison of surgery and omeprazole has shown that these treatments are as effective as each other, at least for the first three years of follow up.<sup>20</sup> There are also convincing data which show that the outcomes of antireflux surgery vary substantially, even in centres of excellence, depending on surgeon experience.<sup>21</sup> This appears to be particularly the case for laparoscopic surgery.

### The place of endoscopy in long term care

Endoscopy is frequently used for routine follow up of patients with reflux disease but data on how this aids patient management are remarkably limited. Consequently, it is not surprising that there is a wide divergence of opinion about how endoscopy should be used. This is important given the relatively high cost and inconvenience of endoscopy in many practice settings.

There is reasonable support for performance of endoscopy on one occasion if the patient history and/or progress on therapy indicates that reflux disease is a longstanding troublesome problem which requires some form of long term drug therapy.<sup>2</sup> This is on the basis that the presence and severity of oesophagitis show no change over at least 15 years in essentially untreated reflux disease patients,<sup>22</sup> so a single adequately performed and reported endoscopy should define risks and guide subsequent management for many years.

### Utility of follow up endoscopy in reflux disease

Barrett's oesophagus is a special case. How much benefit is gained from endoscopic surveillance of Barrett's oesophagus is a particularly vexing question<sup>23</sup> but it would seem imprudent for an individual practitioner not to offer endoscopic surveillance to a Barrett's oesophagus patient on the grounds that it is cost ineffective.

Apart from surveillance of Barrett's oesophagus, there is little justification for repeated endoscopy in treated reflux disease. The absence of symptoms is a relatively sensitive indicator of adequate control of oesophagitis when this has been found to be present previously.<sup>24</sup> Thus symptom recurrence should be taken as an indication of intensification of therapy

rather than endoscopy. Consistent with this, Blustein *et al* found that ongoing management of reflux disease was influenced primarily by symptom status, with little being added by endoscopic findings.<sup>4</sup>

Conflict of interest: This symposium was sponsored by AstraZeneca, makers of omeprazole. The author of this paper has received sponsorship for travel and an honorarium from AstraZeneca.

### REFERENCES

- 1 Dent J. Quadrennial review—gastro-oesophageal reflux disease. *Digestion* 1998;**59**:433–45.
- 2 Dent J, Brun J, Fendrick AM, *et al*, on behalf of the Genval Workshop Group. An evidence-based appraisal of reflux disease management—The Genval Workshop Report. *Gut* 1999;**44**(Suppl 2):S1–16.
- 3 Jian R, Galmiche J-P, Bretagne J-F, eds. Franco-Belgian Consensus Conference. Gastro-oesophageal reflux in adults: diagnosis and treatment. *Gastroenterol Clin Biol* 1999;**23**(suppl 1):S1–320.
- 4 Blustein PK, Beck PL, Meddings JB, *et al*. The utility of endoscopy in the management of patients with gastroesophageal reflux symptoms. *Am J Gastroenterol* 1998;**93**:2508–12.
- 5 Jones RH, Hungin APS, Phillips J, *et al*. Gastro-oesophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. *Eur J Gen Pract* 1995;**1**:149–54.
- 6 Galmiche J-P, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. *Aliment Pharmacol Ther* 1997;**11**:765–73.
- 7 Bytzer P, Havelund T, Møller Hansen J. Interobserver variation in the endoscopic diagnosis of reflux esophagitis. *Scand J Gastroenterol* 1993;**28**:119–25.
- 8 Chiba N, De Gara CJ, Wilkinson JM, *et al*. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997;**112**:1798–810.
- 9 Lundell LR, Dent J, Bennett JR, *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;**45**:172–80.
- 10 Bate CM, Richardson PD. A one year model for the cost-effectiveness of treating reflux esophagitis. *Br J Med Econ* 1992;**2**:5–11.
- 11 Lindberg G. Omeprazole vs. ranitidine in reflux oesophagitis in Sweden. *Pharmacoeconomics* 1994;**5**(suppl 3):27–34.
- 12 Vigneri S, Termini R, Leandro G, *et al*. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995;**333**:1106–10.
- 13 Holloway RH, Dent J, Narielvala F, *et al*. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. *Gut* 1996;**38**:649–54.
- 14 Klinkenberg-Knol EC, Festen H, Jansen J, *et al*. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. *Ann Intern Med* 1994;**121**:161–7.
- 15 Fouad YM, Katz PO, Castell DO. Adding ranitidine at bedtime controls nocturnal gastroesophageal reflux in patients taking proton pump inhibitors twice daily. *Gastroenterology* 1999;**116**:A208.
- 16 Carlsson R, Dent J, Watts R, *et al*, and the International GORD Study Group. Gastro-oesophageal reflux disease (GORD) in primary care—an international study of different treatment strategies with omeprazole. *Eur J Gastroenterol Hepatol* 1998;**10**:119–24.
- 17 Blum AL, Adami B, Bouzo MH, *et al*. Effect of cisapride on relapse of esophagitis. A multinational, placebo-controlled trial in patients healed with an antisecretory drug. *Dig Dis Sci* 1993;**38**:551–60.
- 18 Bardhan KD, Müller-Lissner S, Bigard MS, *et al*. Symptomatic gastro-oesophageal reflux disease: double blinded controlled study of intermittent treatment with omeprazole or ranitidine. *BMJ* 1999;**318**:502–7.
- 19 Lind T, Havelund T, Lundell L, *et al*. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis—a placebo-controlled randomized trial. *Aliment Pharmacol Ther* 1999;**13**:907–14.
- 20 Lundell L, Miettinen P, Myrvold HE, *et al*. Long-term management of gastro-oesophageal disease with omeprazole or open antireflux surgery: Results of a prospective, randomized clinical trial. *Eur J Gastroenterol Hepatol* 2000;**12**:879–87.
- 21 Watson DJ, Jamieson GG, Baigrie RJ, *et al*. Laparoscopic surgery for gastro-oesophageal reflux: beyond the learning curve. *Br J Surg* 1996;**83**:1284–7.
- 22 Isolauri J, Luostarinen M, Isolauri E, *et al*. Natural course of gastroesophageal reflux disease: 17–22 year follow-up of 60 patients. *Am J Gastroenterol* 1997;**92**:37–41.
- 23 Nandurkar S, Talley NJ. Barrett's esophagus: the long and the short of it. *Am J Gastroenterol* 1999;**94**:30–40.
- 24 Carlsson R, Galmiche J-P, Dent J, *et al*. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997;**11**:473–82.