DYSPEPSIA MANAGEMENT, USE OF ENDOSCOPY AND REDUCING DRUG COSTS
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BACKGROUND

Dyspepsia is difficult to define accurately but usually entails persistent or recurrent abdominal discomfort centred in the upper abdomen. These discomforts are often related to food and may also be accompanied by nausea, bloating, flatulence and heartburn.

Approximately 4% of consultations in general practice relate to patients with dyspeptic symptoms, although this represents only a small part of dyspepsia generally. Lydeard and Jones reported a six month prevalence rate for dyspepsia in the community of 38%. Dyspepsia may indicate the presence of a gastric or duodenal ulcer or a gastric carcinoma, although the incidence of both conditions is decreasing. More commonly, however, dyspepsia relates to gastro-oesophageal reflux disease (GORD) or functional dyspepsia, where there is either no definable abnormality, or else an abnormality such as non-erosive duodenitis or histological gastritis, which may not account for symptoms.

INVESTIGATION OF DYSPEPSIA

The general practitioner (GP) has a key role in the health service, by acting as a 'gatekeeper'. This filtering function is important in the management of patients with dyspepsia, since hospital clinics and endoscopy service could not otherwise cope with the large numbers. There are several ways of identifying dyspeptic patients in whom there is a greater chance of a major lesion such as peptic ulcer or neoplastic disease. Patients can be selected for endoscopy or empirical therapy based on analysis of symptoms, age, use of non-steroidal anti-inflammatory drugs (NSAIDs), presence of Helicobacter pylori infection, or a combination of factors.

Age threshold of 45 years

The risk of major lesions such as gastric cancer rises with age and is uncommon below the age of 45 years. Local guidelines introduced within the last 18 months have suggested using 40 years as a threshold for deciding the appropriateness of an endoscopy, although I think this is perhaps too cautious and may lead to too many endoscopies in younger patients with minimal findings (oesophagitis, gastritis, duodenitis or normal result).

Gastric cancers were examined over a six year period (1986 to 1992) in West Gloucestershire, population 330,000, which is similar to that of Morecambe Bay Health Authority. Only 25 of 330 cases occurred in patients less than 55 years of age (Figure 3), and all 25 patients had high risk clinical features including weight loss, dysphagia, anaemia or

patients with a higher chance of significant disease. Such guidelines were generated in 1995 on behalf of Morecambe Bay Health Authority, following discussions between Drs Anthony Adamson (RLI and WGH) and John Keating (FGH) together with district pharmacy advisors. It will soon be time to re-examine these guidelines in the light of new clinical data and national guidelines issued by the British Society of Gastroenterology.
gastrointestinal bleeding, perforation, palpable mass, cerebral metastases and previous gastric surgery (unpublished data). None of these patients presented with 'simple dyspepsia'.

Risks of missing gastric cancer in a patient less than 55 years with 'simple dyspepsia' There are 10,000 deaths from gastric cancers in the UK annually. If the UK population is assumed to be 50 million and 10% of deaths occur in patients less than 55 years (based on West Gloucestershire figures), then there are 1,000 deaths nationally in the younger age group. If half of this group are assumed to present with obvious high risk symptoms and half with 'simple dyspepsia', only 500 cases of gastric cancer in patients with 'simple dyspepsia' less than 55 years would occur nationally. If a GP with an average list size of 2500 patients decided never to endoscope any patient less than 55 years of age without high risk symptoms, he or she would miss only one gastric cancer every 40 years. It is unlikely that an age threshold of 55 years would be widely adopted, but this line of reasoning should at least be reassuring to local GPs. The British Society of Gastroenterology has recently produced guidelines for dyspepsia and is currently recommending an age threshold of 45 years.

Symptoms – discriminant analysis and high risk A patient complaining of typical retrosternal burning chest pain (heartburn) and acid sour taste in the throat either after meals or when lying down, can be assumed with a fair degree of certainty to have GORD, especially if those symptoms respond promptly to acid suppressing drugs. Endoscopy is only required for those with atypical symptoms, a poor response to therapy, or new onset of symptoms after 45 years of age.

Experts have tried to classify patients with dyspepsia based on analysis of symptoms, in order to rationalise investigations and treatment. A clinical label of 'ulcer-like dyspepsia' 'reflux-like dyspepsia' or 'dysmotility-like dyspepsia' is unhelpful in trying to predict the presence of organic disease.

High risk symptoms associated with dyspepsia should alert the clinician to investigate promptly, irrespective of the patient's age. Such symptoms include dysphagia, protracted vomiting, weight loss, anaemia and gastrointestinal bleeding.

Non-steroidal anti-inflammatory drugs (NSAIDs) NSAIDs can cause dyspepsia in the absence of a definable gastrointestinal lesion in approximately 30% of patients. More importantly, they are associated with gastroduodenal erosions, ulcers and ulcer complications such as gastrointestinal bleeding and perforation. Any patient with dyspepsia currently taking aspirin or NSAIDs should be considered for endoscopy, particularly if the clinician wishes to continue treatment with the NSAID.

Helicobacter pylori status Warren and Marshall rediscovered Helicobacter pylori and first suggested its role in the pathogenesis of gastritis and peptic ulcers. Helicobacter pylori represents the most common worldwide chronic infection and is also associated with gastric cancer and certain gastric lymphomas, being recognised as a carcinogen by the World Health Organisation in 1994.

The prevalence of Helicobacter pylori infection increases with age in the general population (Figure 4). It is also associated with poorer socio-economic conditions and thought to be transmitted by a faeco-oral or oro-oral route predominantly in childhood (Figure 5).

Non-invasive tests for Helicobacter pylori infection can be used to screen younger patients (less than 45 years) with dyspepsia in order to make efficient use of endoscopy. Those with negative serology testing, not on NSAIDs and without high risk symptoms do not require endoscopy, since the chance of a peptic ulcer is negligible. Approximately 25% of younger symptomatic subjects will be positive for Helicobacter pylori infection and may potentially have a symptomatic peptic ulcer. It is these patients who should be selected for endoscopy. Screening for Helicobacter pylori infection is not helpful in patients older than 45 years since new onset dyspeptic symptoms would prompt referral for endoscopy anyway.

There are numerous diagnostic tests for Helicobacter pylori which detect antibodies against Helicobacter pylori in saliva, whole blood or serum. Salivary and whole blood agglutination tests yield disappointing results (high false negative and false positive rate). The ELISA-based serology tests give more consistent results, with the Premier test performing best in comparative analysis (sensitivity and specificity between 98 and 100%) Dr David Telford, consultant microbiologist, currently offers this test locally, at a cost of £10-£15. An important consideration, however, is the relative thresholds for requesting a blood test or an endoscopy by a GP. If there is a lower threshold for requesting a blood test compared to an endoscopy, then the positive results for serology can, paradoxically, lead to a greater demand for endoscopy.
The urea breath test is also non-invasive, but is more expensive (around £30) and should be reserved for confirming eradication of Helicobacter pylori when repeat endoscopy is not required\(^\text{19}\). Urea breath tests are not currently available in our area. Follow-up serology is not useful for assessing effective eradication since circulating antibodies to Helicobacter pylori can persist.

**Empirical therapy**

Antacids and H\(_2\)-receptor antagonists can be used empirically without a definitive diagnosis in young dyspeptics\(^\text{18}\), and a short fixed course of the more powerful proton pump inhibitors can act as a clinical trial\(^\text{19}\). Failure to respond adequately to omeprazole or lansoprazole renders a diagnosis of acid-related disease (peptic ulcer or GORD) unlikely. Remission of symptoms negates the need for endoscopy, whilst relapse of symptoms other than clear-cut reflux symptoms prompts the need for a gastroenterological opinion or endoscopy.

A positive result for Helicobacter serology gives the GP two choices: either refer for endoscopy or treat empirically with a course of eradication therapy. A one-week course of triple therapy (approximately £40) initially sounds a more attractive proposition, but most of these patients will not have a peptic ulcer. Helicobacter pylori plays no pathogenetic role in GORD and is not effective in functional dyspepsia, judging from 16 clinical trials. Most of these patients would therefore not respond to an eradication course (except for any placebo effect) and would still need a later endoscopy. Current district recommendations suggest routine treatment of Helicobacter pylori-positive dyspeptic patients with eradication therapy, although I have reservations. The British Society of Gastroenterology has recently published dyspepsia management guidelines (September 1996) recommending serology testing for Helicobacter pylori to rationalise appropriate use of endoscopy in patients less than 45 years, and advising eradication of Helicobacter infection only in those with confirmed duodenal ulcer (DU) or gastric ulcer (GU). Further clinical data in the future may lead to a widening of the indications for Helicobacter pylori eradication therapy.

**Early endoscopy versus empirical therapy**

Cost constraints mean that it is not possible to investigate every patient with dyspepsia, but there is now good evidence from randomized trials that the costs of early endoscopy are lower than empirical therapy. When young dyspeptic patients were randomised to early endoscopy or empirical ranitidine for four weeks, higher patient satisfaction levels and lower global health costs were associated with the former\(^\text{18}\).

**TREATMENT OF PEPTIC ULCER DISEASE**

**Duodenal ulcer**

Traditional treatment with acid suppression involved four- to eight-week healing courses of cimetidine or ranitidine (healing rates of 75% to 90%), or more recently two- to four-week courses of omeprazole and lansoprazole (healing rates of 80 and 96%). Since ninety-five per cent of duodenal ulcers are associated with Helicobacter pylori, and their natural history is dramatically altered if the infection is ‘eradicated’ (Figure 6)\(^\text{19}\), anti-bacterial therapy now represents the most cost-effective management. When the DU is not associated with any high risk features (bleeding or perforation) a one-week course of eradication therapy may be all that is required, provided that symptoms have settled. Although the DU may not have healed at one week, it has a high chance of being healed at four weeks with no further anti-secretory therapy\(^\text{19}\). DU patients taking NSAIDs should be advised to stop the NSAID if possible, although ulcers will heal in response to anti-secretory therapy even if the NSAID needs to be continued\(^\text{19}\).

It is not necessary as a routine to re-endoscope a patient with a low risk DU (no complications) to ensure ulcer healing, or to re-test to confirm eradication of Helicobacter pylori with a urea breath test. Absence of further dyspeptic symptoms and consultations can act as a surrogate marker for efficacy. A bleeding DU should be treated with eradication therapy followed by a further three weeks of proton pump inhibitor. If a negative test for Helicobacter pylori is obtained at least four weeks following the end of this course (urea breath test or endoscopy with CLO test and histology), the chance of ulcer relapse is negligible and long-term maintenance antisecretory therapy is not required.

**Gastric ulcer**

Eighty per cent of gastric ulcers are associated with Helicobacter pylori and these should be treated with an eight-week course of acid suppression, including one week of triple therapy to eradicate the infection. Any NSAIDs should be stopped to aid ulcer healing although GUs can heal with acid suppression with continued use of NSAIDs.

An important consideration in GU management (in contrast to DUs) is the need for biopsies at initial endoscopy, and repeat endoscopy with biopsies at an interval (e.g. eight weeks) to confirm ulcer healing and exclude a malignant lesion\(^\text{20}\).

**Gastritis, duodenitis and functional dyspepsia**

Erosive gastritis is often due to the use of aspirin or NSAIDs, or related to infection with Helicobacter pylori. Treatment should be directed towards eliminating ulcerogenic drugs and eradicating Helicobacter pylori, together with a course of acid suppression. Erosive duodenitis can be treated in the same way as DU, since it probably represents a milder form of the same disease.

Gastritis or duodenitis without erosions may not cause dyspeptic symptoms and these patients fall within the ‘functional dyspepsia’ group. A short course of acid suppression (H\(_2\)-RA or proton pump inhibitor) is worthwhile since patients may be symptomatic of GORD. Other approaches include the use of prokinetic agents (metoclopramide, domperidone or cisapride) or antispasmodic drugs (e.g. mebeverine, peppermint or...
alverine). I have already alluded to the lack of documented efficacy for Helicobacter pylori eradication therapy in these patients from 16 controlled clinical trials.

Which eradication regime for Helicobacter pylori? Earlier regimens were based on two weeks of double therapy with omeprazole plus amoxycillin, giving inconsistent results\(^2\), or else triple therapy based on bismuth salts which is associated with significant side effects\(^2\). In the last three years most gastroenterologists have been recommending one-week courses of triple therapy involving a proton pump inhibitor with two antibiotics. The currently recommended local regimen involves low dose therapy with omeprazole 20mg once daily together with clarithromycin 250mg and tinidazole 500mg, both twice daily. This combination has given an eradication rate of 93% in a clinical trial\(^2\).

There is a pressing need to audit the results in local clinical practice, which may differ from the controlled environment of a clinical trial. Local provision of a urea breath test service for Morecambe Bay area may help to direct us towards more cost-effective therapy. The very least that we need to achieve in local practice is an eradication rate over 90% with a one-week regimen. One-week data for Pyloril-based treatment (ranitidine bismuth subcitrate) is still awaited. Lansoprazole 30mg may be equivalent to omeprazole 20mg, whilst twice daily dosing with a proton pump inhibitor may yield more consistent results\(^2\). A higher dose of clarithromycin (500mg rather than 250mg) may be more effective\(^2\), whilst metronidazole 400mg is equivalent to tinidazole 500mg in tolerability and efficacy at a tenth of the cost\(^2\).

Antibiotic resistance may account for some treatment failures but Dr David Telford has confirmed that local strains of Helicobacter pylori have low resistance rates to antibiotics (metronidazole 14%, clarithromycin 2%, ampicillin 0%, tetracycline 0%).

Gastro-oesophageal reflux disease (GORD), eradication therapy and reducing drug costs It is worth considering the aims of therapy, in order to define cost-effective treatment for the individual. Whilst abolition of symptoms and healing of oesophagitis represent useful markers of efficacy in clinical trials, most patients in clinical practice want sufficient control of their reflux symptoms to allow them to lead a normal life. Physicians should aim for the least expensive tolerated medication sufficient to control symptoms to the patient’s satisfaction (Table 1)\(^1\). Those who develop peptic oesophageal stricture requiring dilatation should have maintenance with proton pump inhibitors to minimise stricture recurrence.

If simple antacids fail to control reflux symptoms, metoclopamide, domperidone and generic cimetidine represent the cheapest options. The next therapeutic step should be low dose proton pump inhibitor (omeprazole 10mg or lansoprazole 15mg) which is considerably cheaper than branded Zantac (ranitidine 150mg bd) although generic ranitidine is expected to enter the market this year. Some patients need standard dose proton pump inhibitors, although there is some evidence that lansoprazole 15mg gives similar symptom control to omeprazole 20mg, with large potential cost savings\(^2\). The newest proton pump inhibitor pantoprazole 40mg is equivalent to omeprazole 20mg in potency with a small cost saving, but not as attractive as lansoprazole 15mg from the viewpoint of cost.

Very few patients require a combination of proton pump inhibitor and prokinetic agent. The expensive prokinetic agent cisapride should probably be reserved for patients who fail on less expensive medication, or those with oesophageal emptying disorders.

Two other groups to target in primary care to reduce drug costs are those patients on longterm acid suppression therapy, usually ranitidine or omeprazole. One group is on longterm therapy to prevent DU recurrence but since effective eradication of Helicobacter pylori virtually eliminates the chance of ulcer recurrence these patients should have triple therapy and have their maintenance therapy discontinued. Most patients will do well whilst some will return for treatment of GORD symptoms. The second group have GORD, but it may be possible to step down their therapy from standard to low dose proton pump inhibitor and convert those on Zantac to generic cimetidine provided there are no important drug interactions. In 1995 one GP practice in West Gloucestershire called up the computer records of all their patients taking omeprazole 20mg od and changed them all overnight onto 10mg od. This radical action prompted 50% of patients to return in need of the original dose, but they achieved an overall cost saving of 25% in this patient group. Whilst not necessarily advocating this unilateral decision-making process without patient involvement, it does illustrate that significant cost savings are possible.

As a senior registrar in West Gloucestershire, I helped to devise an educational programme based on consultant-delivered workshops held in GP surgeries around the county.

### Table 1 Monthly drug costs for maintenance therapy in gastro-oesophageal reflux disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost (28 to 30 days) - £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopamide</td>
<td>10 mg tds</td>
<td>1.80</td>
</tr>
<tr>
<td>Cimetidine (generic)</td>
<td>400 mg bd</td>
<td>6.94</td>
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<tr>
<td>Domperidone</td>
<td>10 mg tds</td>
<td>7.40</td>
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<td>Gaviscon liquid</td>
<td>20 ml qds</td>
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</tr>
<tr>
<td>Cimetidine (generic)</td>
<td>400 mg qds</td>
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</tr>
<tr>
<td>Lansoprazole</td>
<td>15 mg od</td>
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<tr>
<td>Omeprazole</td>
<td>10 mg bd</td>
<td>19.95</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>150 mg bd</td>
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</tr>
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<td>Ranitidine</td>
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<tr>
<td>Famotidine</td>
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</tr>
<tr>
<td>Pantoprazole</td>
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</tr>
<tr>
<td>Lansoprazole</td>
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<td>Omeprazole</td>
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</tr>
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<td>Cisapride</td>
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<tr>
<td>Omeprazole</td>
<td>20 mg bd</td>
<td>71.00</td>
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### Table 1 Monthly maintenance costs in gastro-oesophageal reflux disease

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost (12 months) - £</th>
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<tr>
<td>Lansoprazole</td>
<td>15 mg od</td>
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<tr>
<td>Omeprazole</td>
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<td>Lansoprazole</td>
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<td>Omeprazole</td>
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<td>426.00</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg bd</td>
<td>852.00</td>
</tr>
</tbody>
</table>

Figure 7 Influence of an educational programme on county-wide dyspepsia prescribing costs in West Gloucestershire
We concentrated on appropriate use of endoscopy, relevance and management of *Helicobacter pylori*, and reducing dyspepsia drug prescribing costs. Prescribing data was obtained from the Prescriptions Pricing Authority and a reduction in community dyspepsia drug prescribing costs of 15% was attributable to this educational policy, when compared with East Gloucestershire (Figure 7)**. Extrapolation of these figures to the UK population reveals a potential saving of £50,000,000 per annum.

**ACKNOWLEDGEMENTS**

I'd like to thank both Drs Anthony Adamson and John Keating for their helpful comments, and also Alison Harry for prompting me to complete this article before the turn of the millenium!

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