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Treatment of *Helicobacter pylori* infection: management of patients with ulcer disease by general practitioners and gastroenterologists

G N J Tytgat

Summary

Knowledge of the importance of *Helicobacter pylori* infection is still fragmentary. Currently only a minority of patients with ulcers receive adequate eradication therapy. Ideally there should be no difference in the level of knowledge between general practitioners and gastroenterologists. Yet in practice there is a substantial difference. The results obtained in highly selected clinical trials do not reflect results of practice in the real world. The gap can only be narrowed through careful mass education. The role of testing for *H pylori* infection in primary care practice needs to be clarified and the problem of erratic treatment by general practitioners and specialists needs to be resolved. Adequate response to these problems will require the creation of "regional platforms" where both primary care physicians and specialists decide on empirical therapy, eradication strategy and referral of dyspeptic patients.

Introduction

The spread of scientific information regarding the importance of *H pylori* infection in humans has proceeded at an unprecedented rate. Despite this explosion of information, for many physicians knowledge is still fragmentary and therefore the therapeutic consequences are incomplete, erratic and sometimes non-existent. Theoretically there should be no difference in the level of knowledge and the therapeutic approach to *H pylori* infection between general practitioners (GPs) and specialist gastroenterologists. Yet in practice there is regrettably a substantial difference. The gap can only be narrowed through careful education of both GPs and gastroenterologists given that new strategies are emerging almost daily. The most important question to be answered for GPs is the role of testing for *H pylori* in the management of patients presenting with dyspeptic symptoms or even signs and symptoms of peptic ulcer disease. With the advent of simple office based tests for *H pylori* diagnosis, further studies are warranted on the economics of *H pylori* testing and treatment in patients with suspected but unconfirmed peptic ulcer disease.

Level of knowledge of *H pylori* infection

Data on the level of knowledge of the role of *H pylori* in peptic ulcer disease are still limited.¹ Fendrick *et al* recently interviewed 1350 GPs and internists.² Figure 1 illustrates the use of *H pylori* eradication therapy by GPs and specialists. Gastroenterologists were more aware of the relation between *H pylori* infection and peptic ulcer disease and adapted their practice more quickly to this emerging information.

More recently, Breuer *et al* interviewed a large number of American physicians.³ Table 1 summarises the salient features of that study. It is obvious from these recent data that there are still major differences in the overall appreciation of the importance of *H pylori* infection by GPs and gastroenterologists. More recent evidence indicates that most GPs and gastroenterologists are aware of the causal relation between *H pylori* infection and duodenal ulcer disease, but less so for gastric ulcer disease. However, application of this new information by the former is still insufficient.³

How should peptic ulcer disease be diagnosed?

A minority of patients with dyspepsia seen by GPs have ulcer disease and a genuine ulcer diathesis. Whether symptoms can be used to diagnose peptic ulcer disease accurately, as opposed to functional dyspepsia or other organic diseases, is a matter of controversy. Duodenal ulcer disease can be accurately diagnosed on the basis of symptoms in no more than 25% of cases.⁴ Practically, ulcer disease can only be diagnosed by endoscopy or, rarely now, by radiology. Yet not every dyspeptic patient should undergo endoscopy. Hence, how does the GP distinguish a trivial episode of dyspepsia from a significant one?

An increasing number of GPs favour the so-called test and treat strategy. Accordingly, patients under 45 years of age without alarm symptoms are being tested and *H pylori* eradication therapy is prescribed for those with a positive result. The percentage of those with an ulcer diathesis in the overall population of dyspeptic patients is usually small. Although there are exceptions,⁵ the average figure is around 10%. This suggests that most patients are more likely to have functional dyspepsia. However, so far there is not much evidence from randomised controlled trials suggesting that eradication of *H pylori* is more effective than placebo in relieving dyspeptic symptoms.^{3,6} Despite a plethora of negative efficacy studies and the fact that more than half of the patients will experience recurrent dyspeptic symptoms despite being cured of their infection, many GPs are now willing to go ahead with treatment as they feel that symptoms might improve. There is indeed the occasional patient who experiences prolonged benefit after cure of *H pylori* infection. Moreover, there is also the paucity of alternative effective treatments and this strategy will catch that unknown percentage of patients who have a genuine ulcer diathesis.⁷

A practical consequence of this test and treat strategy is that, for many patients with ulcer

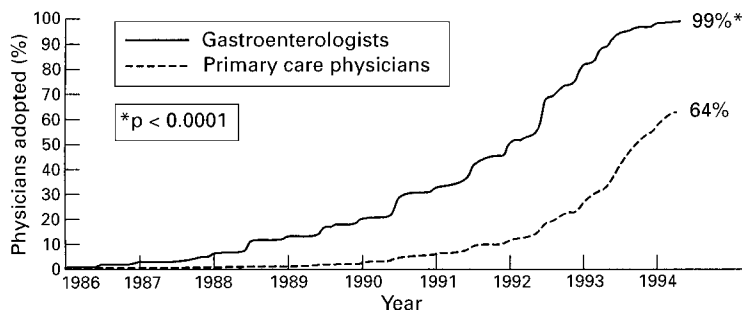


Figure 1 Adoption of *H pylori* eradication therapy and timing of first use by specialty. Adapted from Fendrick *et al.*²

diathesis, no proper diagnosis will ever be reached. This would be perfectly acceptable if appropriate treatment and proper monitoring of its therapeutic efficacy were always available to GPs. This would protect treatment failures from recurrent ulceration and potential complications. Long term data to prove that such a test and treat strategy is indeed realistic and safe are currently lacking. Agréus and Talley⁸ recommend prompt endoscopy for patients with a positive result on *H pylori* testing. If it is not possible/advisable to arrange a prompt endoscopy, they recommend empirical treatment of *H pylori* instead, provided the screening test for *H pylori* is reliable.

Cost-benefit analysis

Several cost-benefit analyses have been published⁹⁻¹⁴ and all came to the conclusion that a test and treat strategy excluding endoscopy is the most cost-effective approach. Yet all those studies are based on the fact that the authors knew/supposed that the patient had ulcer disease. If one wants to restrict therapy only to patients with ulcer disease, then there would have to be a reduction in the cost of endoscopy to make referral for this test cost-effective. Other weaknesses of many of the cost-benefit analyses include the unknown percentage of dyspeptic patients who might improve on being cured of their infection and the fact that many features are difficult to quantify or to evaluate, such as bacterial resistance and the cost of adverse events or side effects—for example, severe diarrhoea, pseudomembranous colitis, ulcer complications after failed cure, etc. Rapidly changing therapeutic strategies also render many calculations obsolete. Finally all estimates reflect practice in a particular geographical area and cannot be extrapolated to other countries.

Table 1 Summary of the salient features of the study by Breuer *et al.*³ In total, 3117 physicians were interviewed

	Gastroenterologists	General practitioners
<i>H pylori</i> is a causative agent in duodenal ulcer	94%	68%
<i>H pylori</i> is a causative agent in gastric ulcer	72%	68%
<i>H pylori</i> is definitely related to gastric cancer	21%	9%
<i>H pylori</i> is causally related to MALT lymphoma	55%	5%
Use of ineffective, unproven regimens (103 regimens in use)	11%	31%

MALT, mucosa associated lymphoid tissue.

Treatment practice in the real world

Highly effective eradication strategies are available and comprise a proton pump inhibitor or ranitidine bismuth citrate with two antimicrobials or quadruple therapy (proton pump inhibitor plus bismuth plus tetracycline plus metronidazole). Although these triple/quadruple drug therapies give excellent results in clinical trials, their efficacy in practice will almost certainly be less. Indeed, the results in highly selected clinical trials do not reflect results of practice in the real world. Penston and Mistry¹⁵ recently evaluated five general practices in Scotland. Fifty six different regimens were used in 154 patients. Two thirds of the patients were not tested for *H pylori* infection before receiving eradication therapy. Half the patients received dual therapy which has now been superseded, 52% complained of symptom recurrence and 47% required further treatment for their symptoms. The results of a recent American study are equally disturbing. One hundred and three different regimens were used and ineffective regimens were prescribed by 31% of the GPs compared with 11% of the gastroenterologists.³

These appalling results should not automatically lead to the conclusion that appropriate treatment by GPs is impossible. Some recent studies have shown equally high cure rates can be achieved by both GPs and specialists when appropriate eradication strategies, even quadruple therapy, are used (Lai *et al*, manuscript submitted).¹⁶ However, it is fair to conclude that we need more comprehensive data on how GPs and specialists, outside the context of a clinical trial, are treating suspected *H pylori* infection. Choice of treatment differs widely depending on the country and also within a particular geographical area. New and more effective therapies, particularly monotherapies, which are easy to take and of short duration, are urgently needed. Until these are available, the only possible way to reduce the chaos and confusion is to create "regional platforms" where both GPs and specialists decide together which treatments to use and how to monitor their efficacy.

Do patients with ulcer disease receive appropriate treatment?

It has now been shown by many studies that cure of *H pylori* infection is equivalent to cure of *H pylori* associated ulcer disease^{17, 18} and that recurrent infection is exceedingly rare.¹⁹ Despite these encouraging data, in reality only a minority of patients with ulcers receive appropriate antimicrobial therapy. According to Penston and Pounder¹⁹ only 9% of the subjects with peptic ulcer disease have received treatment for *H pylori* eradication. These data were derived from more than 150 sampling points in England, Scotland and Wales in 1994. According to Bodger *et al* only 30% of patients with previously documented peptic ulcer disease received *H pylori* eradication therapy.²⁰ This study took place in GP practices in the Leeds area in 1995.

Vreeburg *et al* analysed patients presenting with acute upper intestinal bleeding in the greater Amsterdam area (fig 2).²¹ Only a small

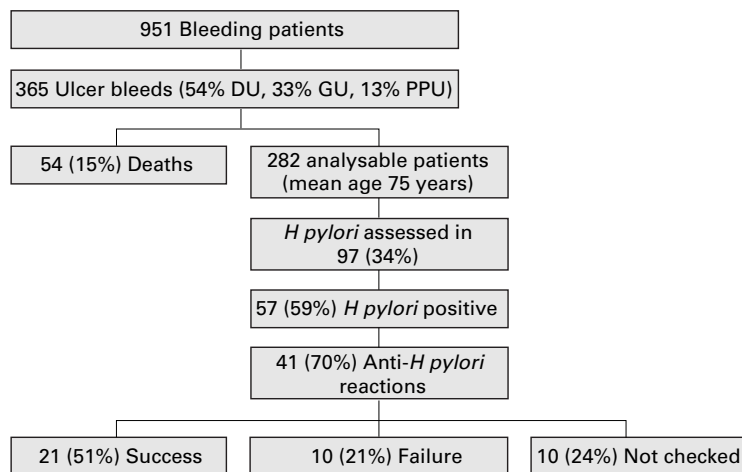


Figure 2 Upper intestinal bleeding. Amsterdam study (1994) including two academic teaching hospitals and 10 regional hospitals (catchment population 1.6 million). DU, duodenal ulcer; GU, gastric ulcer; PPU, prepyloric ulcer.

Reasons for referral to specialist gastroenterologists

- *H pylori* associated refractory ulceration
 - Confirmation of diagnosis
 - Microbial resistance pattern
- Primary *H pylori* negative ulceration
- Recurrent ulceration despite eradication of *H pylori*
 - Idiopathic acid/pepsin hypersecretion
 - Overt/covert use of aspirin or non-steroidal anti-inflammatory drugs
 - Crohn's disease
 - Gastrinoma
- Refractory/complicated ulcer disease

fraction of patients with *H pylori* associated bleeding ulcers ultimately received suitable eradication therapy.

Conclusion

Some experts have expressed the view that *H pylori* infection is simply an eradicable infectious disease which should be eliminated in all those infected. This is quite a shocking idea to many of us, yet this approach needs to be seriously considered by health care providers. In reality we are still far away from this idealised situation.

Without doubt GPs will play a key role in solving the *H pylori* "problem" because they are the ones who see the patients first. Solving the problem will require optimal teaching and education of both GPs and specialists and the creation of regional platforms where the overall approach and the selection of treatment will be decided upon depending on the local antimicrobial resistance patterns.

Although GPs will increasingly treat most of those patients with *H pylori* associated ulcer diathesis, some patients will need to be referred for specialist investigation (summarised in the box). Discovering the cause of ulceration in those patients will undoubtedly require expert endoscopy with multiple biopsies and occasionally gastric secretory and hormonal analysis.

It is probably wise to discourage the use of newer antimicrobial regimens until their effi-

cacy has been established by rigorous studies. This certainly would help to reduce confusion among clinicians. Primary care physicians should concentrate on a few effective regimens which have been approved by the regional platforms. Regular review by the regional platform is obviously essential and includes monitoring of microbial sensitivity and drug availability. Effective education of both GPs and specialists with regard to which treatment to use and when is urgently needed. Further approval of these regimens by the national health authorities may well be the best way to ensure overall good management and compliance.

Several unresolved questions and issues continue to cloud current treatment of *H pylori* infection, including how *H pylori* positive patients with dyspepsia should be treated, how to tackle the link between infection with *H pylori* and gastric cancer in a cost-effective way, and how to encourage physicians to use more effective treatment regimens. The agenda of issues to be resolved remains impressive.

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