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## Occasional viewpoint

# Search and treat strategy to eliminate *Helicobacter pylori* associated ulcer disease

Peptic ulcer disease is a serious disorder affecting many people and carrying substantial morbidity and even mortality as a result of bleeding or perforation.<sup>1,2</sup> The discovery of *Helicobacter pylori* as its main aetiological factor is a major breakthrough in gastroenterology. We can cure patients that before were suffering from a chronic recurrent ailment. After curing the infection, *H pylori* associated ulcers do not recur, nor do ulcer complications.<sup>3</sup> Quality of life improves, use of medication diminishes or stops, and the number of doctor visits, hospital admissions, and absenteeism from work decreases. Curing the infection may even increase life expectancy.<sup>2</sup> Hence treating *H pylori* infection in ulcer patients is associated not only with improved health but also with significant economic benefits. It was demonstrated that the use of acid suppressants decreases significantly in ulcer patients whereas it usually does not decrease in those with non-ulcer dyspepsia.<sup>4-7</sup>

Some have claimed that reflux symptoms and/or reflux oesophagitis may develop in successfully treated patients. Whether this is a true development of a new disease or merely the unmasking of an already present but occult diathesis is controversial.<sup>8,9</sup> This possible disadvantage does not outweigh the benefits of curing the infection in this specific ulcer patient group.

The major clinical discoveries regarding this infection are well known to general practitioners, internists, gastroenterologists, and microbiologists. Unfortunately, implementation of this new knowledge to the level of actually treating the right patients remains problematic. In general it is hard to change physician behaviour.<sup>10</sup> Many ulcer patients even today are still being treated with chronic or on demand acid suppressants, a therapy now considered obsolete.<sup>11,12</sup> Vreeburg *et al* showed that only a minority of patients admitted with an upper gastrointestinal bleed in the Amsterdam area was tested for the presence of *H pylori*, and few were actually offered appropriate treatment.<sup>13</sup> Similar disturbing data were published from the USA<sup>12,14-16</sup> and the UK.<sup>17</sup> But even if the right patients are treated, surveys have shown that many different inappropriate and ineffective treatments are being used.<sup>16-19</sup> Better outcomes therefore also depend on a more general agreement on how to treat *H pylori*. We have recently proposed a logical approach to *H pylori* therapy which combines a regimen based on clarithromycin and one based on metronidazole which, if used consecutively, would come close to the desired 100% cure.<sup>20</sup>

Almost 20 years after the discovery of *H pylori* it is sad to realise that we have failed in treating all patients with chronic (duodenal) ulcer disease. One wonders why. In some countries, organisational problems in the deliverance of proven interventions within the healthcare system have obstructed its appropriate use. Another reason may be that too much attention was given to the role of *H pylori* infection in non-ulcer dyspepsia. In retrospect, it would have been more sensible to first treat peptic ulcer disease completely and to move forward to other indications only after appropriate studies had shown these indications to be cost effective targets for treatment. The confusion caused by the

controversy in eradication studies of functional dyspepsia<sup>21</sup> has drawn the attention of the medical community away from the only real and proven benefit of *Helicobacter* therapy.

Because we have not been able to eliminate ulcer disease, health authorities and insurance companies have become interested in interventions that may help to reach this goal. They also want to address the rapidly increasing and sometimes inappropriate use of long term acid suppression.<sup>17,22</sup>

In this paper we wish to explore what can be done to eliminate ulcer disease. Success depends on the ability to target the treatment to the appropriate population. An asymptomatic subject with *H pylori* infection is unlikely to benefit whereas a patient with proven ulcer disease is very likely to benefit from treatment. Studies have shown that the likelihood of finding an ulcer is slightly higher in patients with ulcer-like dyspepsia compared with patients with dysmotility or reflux-like dyspepsia.<sup>23,24</sup> If in a target population the pretest likelihood for ulcer disease is higher, the treatment is more likely to be cost effective (fig 1). The essentials of disease management in ulcer disease have been described previously.<sup>25</sup> Here we will focus on ways to implement *H pylori* therapy for the only group of patients that really needs it: those with proven ulcer disease. Treating other larger groups of subjects only defer us from reaching that goal. The purpose is to search for ulcer patients systematically and treat them. We call this "search and treat" strategy. We will discuss some of the options and results of pilot projects testing such programmes.

### Case finding strategies

Although many patients are being treated for *H pylori* infection, most are suffering from functional dyspepsia<sup>17</sup> and it is doubtful if many of these patients or society as a whole will benefit from this approach.<sup>4-7,21</sup> Only few of those who present with new dyspepsia today are indeed ulcer patients; most have a different clinical entity unrelated to *H pylori* infection. The role of *H pylori* in functional dyspepsia is either small or non-existent.<sup>21</sup> Test and treat strategies in young dyspeptics <45 years were introduced as a method of decreasing the workload and

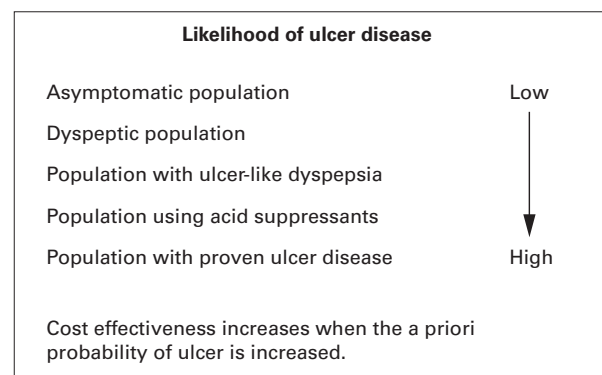


Figure 1 Likelihood of ulcer disease.

saving money in the workup of dyspepsia.<sup>26</sup> Although several studies have now shown that test and treat strategies have a similar (dyspepsia) outcome as prompt endoscopy in uninvestigated dyspepsia the method was not superior to endoscopy in curing ulcer patients. In primary care, unlike the situation in secondary care, dyspepsia has a good prognosis<sup>27</sup> and the majority of patients become asymptomatic within several weeks after any treatment.<sup>28-29</sup> We need to realise that most dyspepsia in primary care is self limiting! Antibiotics may thus be a rather expensive alternative to an antacid, prokinetic, or H<sub>2</sub> receptor antagonist on first presentation.<sup>25-30</sup> It is also for this reason that the European Society for Primary Care Gastroenterology declines the use of test and treat for a first presentation of dyspepsia.<sup>31</sup> The “test and treat” approach is more appropriate in the subgroup with long term or recurrent dyspepsia.<sup>25-31</sup>

In western Europe, *H pylori* infection is rapidly disappearing. Only a minority of young adults are still infected and at risk of occurrence of ulcers, and hence the incidence of ulcer disease is low.<sup>32</sup> As the problem of ulcer disease in young people (the case load) is relatively small, treatment of *H pylori* should not have a prominent role. Because of the low number of incident ulcer cases, any strategy aimed only at this younger age group (<45 years) will not significantly decrease the burden of ulcer disease for society. If the aim is to eliminate ulcer disease, we need to focus on the prevalent cases.<sup>25</sup> As this is a chronic disorder, older people that had their first ulcer 5, 10, 20, or 30 years ago must still be considered ulcer patients.<sup>33</sup> Together they form a large pool of patients. Many have adjusted their lives and have symptoms from several weeks to several months per year and absenteeism from work is common. They follow a diet and use medication regularly. They have adjusted their life to their symptoms and sometimes no longer consider themselves patients. Their quality of life is negatively influenced even while taking maintenance therapy. Usually their ulcers were diagnosed in the past and no additional resources are required for further clinical investigations. We only need to search out these individuals and inform them of the new treatment.

Another possibility is to inform the public directly through the lay press. For example, an “ulcer awareness week” was organised in the USA in August 1999. It was hoped that ulcer patients would seek medical attention after being informed about *H pylori*. However, a true and systematic elimination of the pool of prevalent ulcer cases will only be possible by a combined systematic review of the medical history of large groups of people, coordinated preferably by health authorities. Such disease management programmes will almost certainly turn out to be cost effective and will improve the health and well being of the target population. Economic gains will be reached through a decrease in the expenditure on acid reducing drugs,<sup>4-7</sup> a decrease in absenteeism from work, a reduction in doctor visits, and in the long run in a decrease in hospital admissions for ulcer bleeding or perforation.<sup>3</sup>

Health authorities are responsible for the coordination and elimination of other infectious diseases such as tuberculosis or syphilis. Their task in fighting these diseases is different from the work of the physician who treats a single infected patient. The physician is responsible for his own patient but not for public health and the measures needed to search out other infected patients. The medical profession however has to inform the health authorities of the problem of ulcer disease. We need to promote the idea that this is a public health issue. Once health authorities and other payers discover that this will not only improve health (by eliminating a chronic recurrent disease) but also save money, they are likely to initiate nationwide implementation strategies at the population level.

The organisation and funding of health care in European countries is so different that a pan-European approach is impossible. The optimal way to implement “search and treat” will therefore be different throughout Europe.

### Targeting patients with an ulcer history

The best way to target antibiotic therapy is to give it to those patients with a proven ulcer diathesis. A primary care physician can search his practice for patients with ulcer diathesis and offer them treatment. Many practices today have diagnostic computer databases and can easily produce lists of patients with an ulcer history. Otherwise, a manual search of the patient files is needed. The health authorities could sponsor a “visiting physician” to perform this case finding. The department in charge of fighting infectious diseases from the local health authority, or a nationwide or regionalised task force could perform this task on a project basis. Treatment with adequate antibiotic regimens, according to a fixed protocol,<sup>20</sup> is obligatory for a favourable outcome. Commercial companies have already offered such search services (for example, for hypertension, high cholesterol levels, ulcer disease, etc) to individual physicians and pharmaceutical companies.

The majority of patients identified with a history of ulcer disease will still be infected and can probably be treated without prior testing for *H pylori*. Prach *et al* found that in a cohort of 145 patients receiving long term H<sub>2</sub> receptor antagonists for chronic duodenal ulcer disease only 11.7% were *Helicobacter* negative,<sup>34</sup> a value close to the 10% we found in our study<sup>35</sup> and the 13% in another Dutch study.<sup>36</sup> Cost effectiveness and decision analyses also suggest that physicians can give antibiotics to patients with an ulcer history without a prior diagnostic test.<sup>37-38</sup>

Our previous study in 10 primary care practices showed that such a strategy is feasible, cost effective, and that it improves the health of the target population.<sup>35</sup> We achieved a 94% intention to treat cure rate. After six months, >90% of patients had stopped taking acid suppressants. Similar cost savings were reported from the USA.<sup>39</sup>

### Targeting patients who use acid suppressants

If it is not considered feasible to search for patients with a history of ulcer disease, one can take advantage of the fact that most (symptomatic) patients with ulcer diathesis use acid suppressants. Several studies have shown that between 0.82% and 4.4% of the population in western Europe are taking these drugs long term.<sup>36-40-44</sup> UK studies showed that about one third of patients that regularly use acid suppressants had proven ulcer disease.<sup>40-42</sup> A study performed in the Amsterdam area found a rate of 39.2%,<sup>43</sup> whereas a study in central Holland found a lower rate of 18%,<sup>36</sup> similar to that found in the south (20%).<sup>45</sup> Furthermore, many patients use these drugs without a formal diagnosis (endoscopy or barium meal)<sup>34-38-43</sup> and a significant percentage of such chronic and uninvestigated patients will probably also suffer from recurrent ulcers. It is therefore reasonable to target a population of regular acid suppressant users with antibiotics as many will benefit.

The advantage of this approach is that the search can easily be computerised. Those using over the counter medications will not be identified but one can argue however that the more severely symptomatic patients will be found and therefore the impact on quality of life and cost savings will be greater.

A disadvantage of this strategy is that patients with other causes of dyspepsia, mainly reflux disease, are also identified. One can choose to search the medical history of every individual who uses these drugs and then only treat or “test and treat” those with documented ulcer disease. One can

also choose to do a "test and treat" strategy in the total group, thereby including patients with reflux disease. There are examples of both strategies in the literature.

Cottrill identified 161 patients using H<sub>2</sub> receptor antagonists long term and subsequently 64 with proven ulcer disease were randomised to receive one of two anti-*H pylori* therapies. He documented health benefits and substantial economic savings.<sup>46</sup> A small pilot study by Hippisley-Cox and Pringle documented similar results in 16 ulcer patients treated with antibiotics compared with a control group of 15 patients who continued acid suppression.<sup>47</sup> In a small open study, 40 chronic users were identified with a history of ulcer disease but only 29 agreed to undergo serological testing. Of 20 (69%) who tested positive, only 18 were given antibiotics. In 76% in whom eradication was successful, symptoms disappeared completely and medication was no longer necessary.<sup>41</sup> Forrest *et al* also described a favourable outcome of this strategy in former ulcer patients using acid suppression long term.<sup>6</sup>

In the Netherlands, de Wit *et al* found that 2.8% of patients from 13 general practitioners were using acid suppressants long term<sup>36</sup> and they searched their medical records. Thirty five per cent had never been investigated but 18% had documented proof of ulcer disease. They tested these ulcer patients for *H pylori* infection and treated those infected. The cure rate or quality of life was not measured but in those who were treated, approximately one third stopped taking medications. Their prospective study showed that implementation had several problems, which were similar to the problems in the UK studies we described above.<sup>6 41 46 47</sup> Twenty one per cent could not be convinced of the benefits of antibiotics and refused testing. Another 8% who tested positive refused treatment. It was clear that patients were hesitant to stop maintenance therapy. It is an ethical dilemma whether a physician should withhold further prescriptions of acid suppressants if a patient keeps refusing the evidence based antibiotic alternative. These data suggest that the success of a systematic "search and treat" strategy may be improved when it is accompanied by a publicity campaign in the media.

In two American studies, the medical history of chronic users of acid suppressants was studied. Patients with ulcer disease as well as functional dyspepsia received antibiotics but patients with reflux disease were excluded. This approach also reduced pharmacy costs.<sup>7 48</sup>

Joosen *et al* chose a different approach.<sup>45</sup> They searched the computer of two regional pharmacies for patients who regularly used acid suppressants and performed a test and treat strategy in the total population, independent of clinical diagnosis. A validated serological ELISA assay was used<sup>49</sup> to ensure that *Helicobacter* negative persons did not receive antibiotics. A media campaign in the local papers supported the project and they documented a high compliance. As expected, the largest improvement in quality of life occurred in those with a history of ulcer disease but some positive effects were also found in patients with uninvestigated dyspepsia or chronic non-ulcer dyspepsia. This study included a cost effectiveness analysis and it was demonstrated that the costs of the programme (cost of serological testing and antibiotic treatment) were balanced by a significant reduction in the use of medication in the target population after only nine months. These results need to be replicated elsewhere in a larger group of patients but it is likely that such projects, which are easily implemented, are cost effective and lead to improved health within one year of follow up. The cost effectiveness increases when the population which uses acid suppressants has a higher percentage of patients with documented ulcers. The advantage of this approach is that medical

records do not need to be studied because all *H pylori* infected chronic users are treated. It simplifies the procedure. The disadvantage is that chronic users without ulcers are also treated. Some of these have functional dyspepsia and may or may not benefit.<sup>21</sup> Others will have reflux disease. Based on the data of Kuipers and colleagues,<sup>50</sup> who showed that *H pylori* positive reflux patients who use acid suppression long term tended to progress to gastric atrophy, we feel that this is not a problem and that it may even lead to a better long term outcome. This issue however remains controversial<sup>8 9</sup> but there is growing support for the treatment of *Helicobacter* infection in chronic reflux disease.<sup>51</sup>

## Conclusion

Test and treat strategies in young dyspeptics were not designed to specifically reduce the burden of ulcer disease. The prevalence of *Helicobacter* infection in young subjects is low and is still declining; the incidence of ulcer disease is therefore low. Most cases of ulcer disease occur in older people; ulcer disease has a high prevalence. There is a large pool of people who have suffered from a documented peptic ulcer in the past and most are still intermittently symptomatic. In order to decrease the prevalence of ulcer disease we need to promote case finding. Only "search and treat" strategies will help us to eliminate ulcer disease. These can focus on patients with an ulcer history or on populations who regularly use acid suppressants. Such strategies, which may be initiated by health authorities or insurance companies, are likely to be cost effective and lead to improved health of the target population. They are easy to implement and more effort should go into such systematic case finding at the population level.

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