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Helicobacter pylori—reflections for the next millennium

G N J Tytgat

Introduction

The unsurpassed speed with which new information has been collected over the past two decades is bound to slow down. Much has been discovered and leading microbiologists are moving to other helicobacters and homing in on other parts of the body, particularly the biliary and intestinal tract. Yet knowledge of the *Helicobacter pylori* genome will continue to stimulate further *H pylori* related research; furthermore, the vaccination programme will keep the basic and clinical researchers busy for some time.

This overview will elaborate on some aspects of further developments, in full awareness of the limitations and hazards involved in speculating about the future.

Disappearance of *H pylori* and *H pylori* associated peptic ulcer disease

In the Western developed world at least, but perhaps also on a global scale, *H pylori* infection is disappearing spontaneously at a surprisingly rapid rate. Several direct and indirect findings support this observation.

Many clinicians have indeed observed that *H pylori* associated peptic ulcer disease is becoming a rare event. In the Amsterdam unit very few new *H pylori* associated duodenal ulcers are currently seen and *H pylori* associated gastric ulcers have almost vanished. This same trend has been observed by El-Serag and Sonnenberg¹ and by Cutler.² The average number of patients that could be enrolled per month per research centre in the USA in various trials decreased from 0.82 in 1994 to 0.25 in 1996. Similar findings were observed in the

United Kingdom by Banatvala *et al.*,³ in Finland by Kosunen *et al.*,⁴ in The Netherlands by Roosendaal *et al.*,⁵ and in many other countries. The possible causes of *H pylori* disappearance may well remain speculative (box 1).

The consequences of the disappearance of *H pylori* associated peptic ulcer disease (PUD) are manifold. Firstly, the percentage of non-*H pylori* associated PUD is bound to rise. Indeed almost half of the (presumably) non-drug induced duodenal ulcers in the USA currently seem to be non-*H pylori* related.⁶⁻⁸ Figure 1 attempts to explain this phenomenon.

Secondly, as the percentage of ulcer patients decreases in the various eradication trials, the cure rates are bound to deteriorate. *H pylori* eradication is in general easier in ulcer patients than in those with chronic dyspepsia. The reasons are still speculative: more virulent, rapidly proliferating organisms living closer to the epithelial surface of the antrum are more readily killed by antimicrobials, better compliance of ulcer patients, etc.

Thirdly, the disappearance of ulcer disease seems to correlate with a rise in gastro-oesophageal reflux disease (GORD).^{1,9} Again, only hypotheses can be offered to explain this phenomenon: healthier stomach with higher acid production; higher body weight; higher fat consumption; more sedentary life style; etc. It is now clear that disappearance of corpus inflammation with suppressed parietal cell function often leads to increased acid production and unmasking of reflux disease.^{10,11}

The “test and treat” puzzle

The vexing issue of appropriate management of infected dyspeptic patients has given way to practical and economic arguments that support a “test and treat” approach. So far almost all guidelines seem to support a test and treat, or “test and endoscope” strategy, early in the approach to the patient with dyspepsia. The justification of this advice is rather weak except in areas where a high percentage of *H pylori* positive dyspeptic patients suffer from PUD, as occurs in Scotland.¹² However, for areas where the percentage of ulcers is much lower and closer to or less than 10%, it becomes highly dubious whether such a test and treat strategy can be defended, as only a limited percentage (20% at most) of such patients will ultimately become symptom-free. It is understandable that many primary care physicians and specialists are losing interest in the test and treat

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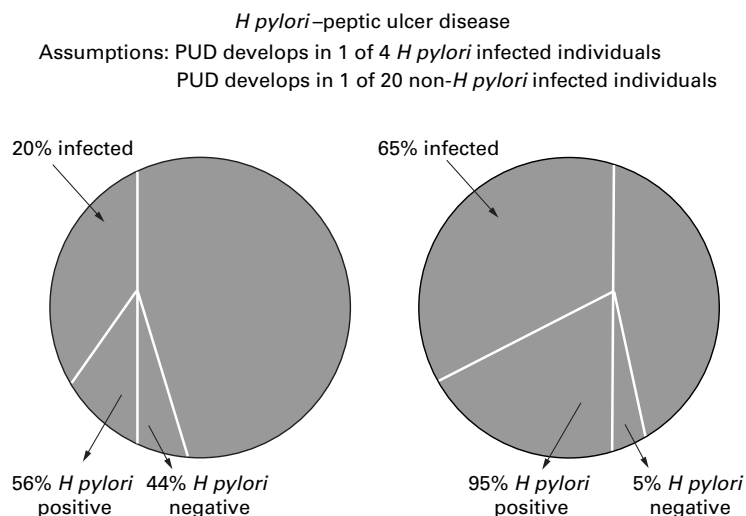


Figure 1 Schematic illustration of the percentage of *H pylori* associated peptic ulcer disease (PUD) in a population depending on the background infection rate.

Abbreviations used in this paper: PUD, peptic ulcer disease; GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.

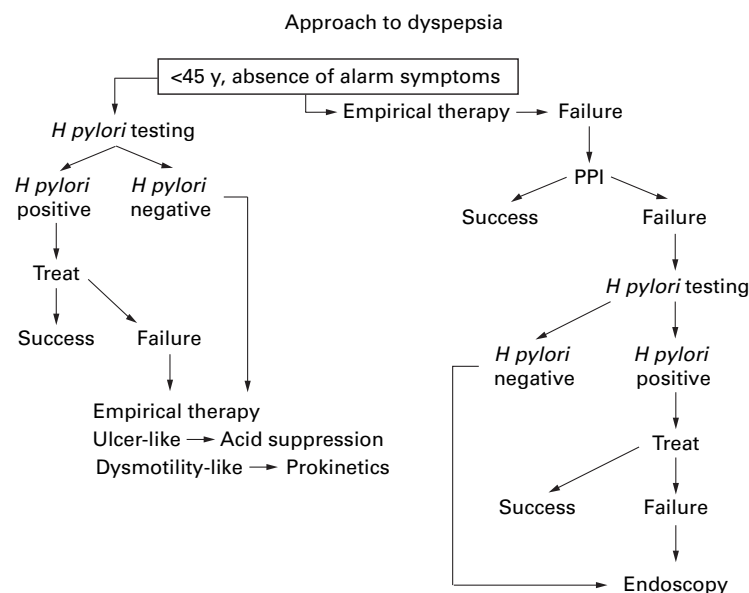


Figure 2 Schematic approach to dyspepsia. Left: *H pylori* testing early in the work up of dyspeptic patients; right: *H pylori* testing late in the work up of dyspeptic patients.

strategy because of these disappointing results, and move *H pylori* testing to the far end of the algorithm (fig 2).

Routine practice becomes even more complicated because no easy way of monitoring treatment is available. The recommended urea breath testing is not widely available and few governments have so far agreed to reimburse general practitioners. Perhaps monitoring treatment with faecal *H pylori* antigens or serological titres will become the method of choice in the future.

Asymptomatic infected subjects are the next large potential target for “testing and treating”. Quantitative approaches to “risk stratification” need to be developed to identify high risk groups which might benefit from cure, particularly through a reduction in their risk of gastric cancer. While such groups are being identified and the economic advantages to society of curing their infection are being quantitated, incentives will increase for the development of effective monotherapies that can be applied safely on a broad scale for population treatment strategies.

A way to predict which *H pylori* carriers will ultimately develop neoplasia will remain an important challenge for years to come. Better understanding of the relation between *H pylori* and cancer of the gastrointestinal tract is

Table 1 *H pylori* eradication treatment

Primary resistance	Regimen	Efficacy range
MET <30%	PPI-CLA-AMO	85–95%
CLA <15%	PPI-CLA-MET	85–95%
	RBC/BIS-CLA-MET	85–95%
	PPI-BIS-TET-MET	85–95%
MET >30%	PPI-CLA-AMO	85–95%
CLA <15%	RBC/BIS-CLA-AMO	85–95%
	PPI-BIS-MET-TET	50–95%
MET >30%	PPI-BIS-TET-MET	50–95%
CLA >15%		

MET, metronidazole; CLA, clarithromycin; PPI, proton pump inhibitor; AMO, amoxicillin; RBC, ranitidine bismuth citrate; BIS, bismuth; TET, tetracycline.

Box 1 Putative mechanisms responsible for decreasing prevalence of *Helicobacter pylori*

- Improved hygiene
- Improved nutrition during childhood
- Smaller family size
- Larger time interval between (fewer) children
- Increase in consumption of antimicrobials

needed to help to develop preventive measures and appropriate interventions.

Further investigations are required concerning the:

- mechanisms by which *H pylori* predisposes some individuals to gastric cancer; in particular, interactions with genetic, environmental, and dietary factors;
- assessment of the reversibility of cancer associated abnormalities (e.g., hypochlorhydria, atrophy, and intestinal metaplasia) by eradication of *H pylori*;
- development of non-invasive means of identifying *H pylori* positive subjects at high risk of developing cancer in order to target eradication therapy, which would be cost effective and desirable. Markers could include family history of gastric cancer, serum pepsinogen I, serum IgG antibodies to *H pylori* CagA, and serum gastrin.

Optimisation of anti-*H pylori* treatment

A universally acceptable antimicrobial treatment scheme will probably never be realised; not all drugs are globally available or affordable and antimicrobial resistance patterns vary widely. The choice will remain for some time between bismuth based triple therapy, proton pump inhibitor (PPI) based triple therapy, and quadruple therapy (table 1).

Issues to be debated include:

- The (ir)rationale of combining the two most important antimicrobials in the initial therapeutic approach.
- Geographical monitoring of the antimicrobial resistance patterns.
- Choice of back up therapy in case of failure.
- The appropriate duration of treatment. As further results become available, it would seem that a differentiated approach is reasonable, limiting treatment to seven days in ulcer patients and extending treatment to 10–14 days in patients with chronic gastritis with/without dyspeptic complaints.
- The intensity of patient instruction and the elimination of confounding or interfering factors such as premedication with acid suppressants (with subsequent clearance of the antrum and colonisation of the corpus) or interference with aspirin.
- Simplifying the treatment, which should become more patient friendly through production of prepacked strips or perhaps combination pills.

Box 2 gives recommendations to limit the induction of antimicrobial resistance.

Box 2 Recommendations to limit/prevent induction of antimicrobial resistance

- Avoid suboptimal treatment
- Avoid combining the two most efficacious antimicrobials (clarithromycin and imidazole); decide on a back up regimen before starting treatment
- Use nitazoxanide instead of metroidazole/tinidazole (?)
- Include bismuth to prevent/overcome resistance (?)
- Prolong treatment duration for non-ulcer patients (?)
- Avoid concomitant use of aspirin/non-steroidal anti-inflammatory drugs (?)
- Attempt to attack sanctuary sites. Use solutions of antimicrobials (amoxicillin) to reach high concentration in corpus/fundus
- Create regional platforms of primary care physicians and specialists to design optimal local strategies

Strategies for managing patients who fail initial treatment require better design and universal agreement, as do the eradication practices in areas where antibiotic resistance is rampant.

Consequences of H pylori cure

A clinically relevant consequence of *H pylori* cure relates to the enhanced acid secretory potential of the healthier non-inflamed human stomach. As stated above, this may contribute to unmasking or induction of reflux symptoms and GORD. Another consequence relates to the apparent decrease in acid suppressant efficacy of PPIs and to a lesser extent, H₂ receptor antagonists. This may have practical consequences. In a recent large study involving 971 patients with moderately severe reflux oesophagitis, four weeks' treatment with pantoprazol 40 mg had a significantly better cure rate in *H pylori* positive patients than in *H pylori* negative ones.¹³ A similar effect was seen with PPI treatment in non-steroidal anti-inflammatory drug (NSAID) induced ulceration.¹⁴ The potentiation of PPI efficacy in *H pylori* infection does not contradict the findings of the Hong Kong group,¹⁵ who showed a lower risk of NSAID induced damage after *H pylori* cure compared with *H pylori* infected gastritis.

The gastric cardia

Two features caused increased interest in the cardia: firstly, the recognition of a rapidly rising incidence of adenocarcinoma in the area of the gastro-oesophageal junction; and secondly, the discovery of frequent inflammation (carditis) and intestinal metaplasia within the cardiac mucosal rim. On the one hand, one should distinguish inflammation (carditis) and intestinal metaplasia in "genuine cardiac mucosa" adjacent to the squamocolumnar mucosal junction, and, on the other, columnar metaplastic

mucosa developing as a consequence of destruction of squamous mucosa within the setting of reflux induced damage. "Carditis" is commonly present in adults together with a high frequency of intestinal metaplasia. The crucial issue concerns the pathogenesis of this "carditis" and "cardiac intestinal metaplasia". Carditis is usually associated with *H pylori* infection, usually without much evidence of GORD. If carditis is essentially an infectious disease, cure of the *H pylori* infection should in principle lead to regression of the inflammation and prevention of further progression of metaplasia. These recent discoveries generated more questions than answers: Does carditis influence sphincter function? Does carditis have any effect on reflex relaxation of the upper part of the stomach and of the sphincter itself? Why is *H pylori* associated cancer more common in the distal part of the stomach and not linked to cancer in the area of the cardia? What is the effect of profound acid suppression on *H pylori* carditis and intestinal metaplasia? Is similar worsening seen during acid suppression as in the gastric corpus or does one find improvement, similar to that usually observed in the antrum? Does inflammation in the cardia itself induce a particular symptom pattern of epigastric burning? These and many more questions fill the agenda for detailed meticulous clinical, histopathological, manometric, hormonal, and electrophysiological studies.

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