Science, medicine, and the future

Helicobacter pylori and gastric diseases

Martin J Blaser

The isolation of *Helicobacter pylori* from clinical specimens by Marshall and Warren 15 years ago¹ launched revolutions in gastroenterology and microbiology.²⁻³ Like other revolutions in history, the original directions of the *H pylori* story have changed in response to conflicting ideologies, observation, and practices. Currently, enthusiasts, drug companies, and the lay press are putting pressure on physicians to eliminate *H pylori* from all patients, symptomatic or not, in whom it is detected. There is little evidence that this is appropriate, and management will continue to change as new knowledge emerges and socioeconomic environments change in ways that are relevant to *H pylori* and clinical medicine. This article looks at past and current trends to anticipate the future of these common bacteria and the disorders associated with them.

Changing epidemiology of *H pylori*

H pylori is one of a large family of related bacteria that are well adapted to persist in the stomachs of vertebrates for the life span of their hosts. It is likely that *H pylori* has colonised our stomachs since well before we became humans.⁴ Studies of primates and human populations in developing countries suggest that, until the last century, nearly all humans carried *H pylori* or closely related bacteria in their stomachs. *H pylori* can thus be regarded as indigenous or “normal” flora, which most humans acquire within the first few years of childhood and then carry for life.

With socioeconomic development, fewer children are acquiring *H pylori*.⁵ This is a worldwide phenomenon that seems to have preceded the introduction of antibiotics, although it may have been accelerated by their widespread use. The reasons for the decline in the prevalence of *H pylori* colonisation are unknown. Improved nutrition and clean water have been proposed. An alternative hypothesis is that most transmission is from child to child and that declining family size reduces the opportunity for transmission and increases the age of acquisition.

In developed countries, for perhaps the first time in the human experience, large numbers of people are now passing their lives without *H pylori* colonisation. This is a crucial observation with considerable relevance for understanding the changing pattern of gastrointestinal diseases.

Possible future developments

Changing epidemiology of upper gastrointestinal diseases (peptic ulceration, oesophageal and gastric adenocarcinoma, gastro-oesophageal reflux disease and sequelae) with changing prevalence of colonisation with *Helicobacter pylori*

Recognition of host factors that predispose to diseases induced by *H pylori*

Definition of genetic characteristics of *H pylori* that are associated with significant variance in risk of disease

Vaccinations against certain diseases based on specific interactions between *H pylori* and host

Colonisation of some hosts with strains of *H pylori* with low virulence to reduce risk of particular diseases

Microbiology of *H pylori*

Genetic studies indicate that *H pylori* strains are enormously diverse.⁶ This diversity reflects the bacteria's ancient ancestry, its niche in varied human populations, its large numbers in colonised hosts (about 10⁸-10¹⁰ organisms per stomach), its ability to mutate over decades of colonisation of a single host, and the ease with which it exchanges genes with other *H pylori* strains.

The key question is whether any of the diversity is of clinical importance. Recent work suggests a qualified “yes.” Three different genetic loci have been identified—*cag*, *vacA*, and *iceA*—for which people harbouring particular alleles have different risks of disease.⁷ In Western countries, a person colonised with a *cag*⁺, *s1a vacA*, *iceA1* strain is more likely to develop duodenal ulceration than a person harbouring a *cag*⁺, *s2 vacA*, *iceA2* strain. These markers are not fully independent of each other and, importantly, are not absolutes but reflect degrees of risk (fig 1). In the future, knowledge of *H pylori* genotypes could help to identify people at risk of particular diseases.

Division of
Infectious Diseases,
A-3310 Medical
Center North,
Vanderbilt
University School of
Medicine, 1161 21st
Avenue South,
Nashville, TN
37232-2605, USA
Martin J Blaser,
director

Martin.Blaser@
mcmail.vanderbilt.edu

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Fig 1 Model of interactions of polar forms of *Helicobacter pylori* with human gastric mucosa and consequent pathophysiology. With highly interactive strains (such as *cag*⁺, *s1a vacA*, *iceA1* genotype), population structure is weighted toward proximity to the mucosa and there is high impact on host tissues, resulting in intense inflammation and host signals (such as changes in gut nutrients, pH, and motility); a regulated dynamic equilibrium between the microbial population and host response has been proposed. Induced changes in host physiology, immune response, and cellular proliferation influence risk of particular diseases. Less interactive strains of *H pylori* (such as *cag*⁻, *s2 vacA*, *iceA2*) colonise in lower numbers and with populations preferentially distributed towards the lumen. These populations are also in equilibrium with the host, but with less "gain" and less serious pathophysiological consequences. Hosts may carry both populations simultaneously

Relation of *H pylori* to disease

Everyone who carries *H pylori* in their stomach develops a cellular infiltrate in their gastric mucosa, termed chronic gastritis. In most people this causes no symptoms, but *H pylori* carriers do have an increased risk of developing peptic ulcer disease (about threefold to 10-fold) and adenocarcinoma of the antrum and body of the stomach (twofold to 10-fold). Elimination of *H pylori* with antimicrobial treatment heals the ulceration and substantially reduces the risk of recurrence.⁸

Peptic ulcer disease and gastric cancer involving the antrum and body have been declining in the 20th century in precisely those parts of the world in which the prevalence of *H pylori* colonisation has declined, and much evidence suggests the events are related. Carriage of *H pylori* also increases the risk (about sixfold) of developing primary non-Hodgkin's lymphomas of the stomach (MALTomas).⁹ Elimination of *H pylori* markedly attenuates the course of low grade MALTomas.¹⁰

Non-ulcer dyspepsia occurs roughly as often in *H pylori* carriers as in non-carriers. Non-ulcer dyspepsia is a heterogeneous group of disorders, and if *H pylori* plays any role in this it affects only a minority of patients.

While ulcer disease and distal gastric adenocarcinomas have become less common as *H pylori* is disappearing, a new group of diseases has been increasing rapidly in Western countries—gastro-oesophageal reflux disease and its sequelae, Barrett's oesophagus, and adenocarcinoma of the (distal) oesophagus. The incidences of adenocarcinoma of the oesophagus and

gastric cardia are increasing rapidly in several Western countries,¹¹ and in white American men now exceed the prevalences of squamous cell oesophageal cancers and distal gastric adenocarcinomas respectively. Their rapid rise indicates a strong environmental cause, and there is no evidence that the epidemic is abating.

A key question, therefore, is whether the advent of these diseases is related to the simultaneous fall in carriage of *H pylori* (fig 2). Evidence links the lack of *H pylori* with gastro-oesophageal reflux disease, Barrett's oesophagus, and the risk of adenocarcinoma of the oesophagus and gastric cardia.¹²⁻¹⁴ In particular, it seems that *cag*⁺ strains exert a protective effect whereas *cag*⁻ strains have essentially no effect.^{14 15} These preliminary observations need confirmation but, if correct, suggest that clinicians should not eliminate *H pylori* from everyone, as they will be trading a decreased risk for certain diseases (peptic ulcers, adenocarcinomas of gastric antrum or body) with increased risk for others.

The future

Diseases

Because the presence of *H pylori* in the stomach is related to several different clinical entities, I will predict critical issues for each.

Peptic ulceration—This is increasingly becoming a disease of the elderly in developed countries, with non-steroidal anti-inflammatory drugs implicated as a major cause. All patients should be investigated to determine whether they are carrying *H pylori*, which if present should be eliminated. Regardless of the risk of other diseases, removal of *H pylori* should confer more short term and long term benefit than harm. In developing countries, where the age of acquisition of *H pylori* is increasing, the incidence of gastric ulcer and distal gastric cancers is likely to fall and that of duodenal ulceration to increase.¹⁶

Adenocarcinoma of lower (distal) stomach—The major challenge is to understand the pathogenesis of this disease so that people at high risk of developing cancer can be identified and the disease prevented or treated at an early stage.¹⁷ The dominant form, the "intestinal type," seems to be related to the development of

Fig 2 Changing incidence of acquisition of *H pylori* and gastric cancers in Western countries. Colonisation with *H pylori* seems to have been nearly universal among adults before 1800 and then began to diminish until the present, when <20% of children are colonised. Concomitant with the drop in *H pylori* colonisation, the incidence of adenocarcinoma of the antrum and body (distal stomach) has declined, but adenocarcinomas of the cardia (proximal stomach) and distal oesophagus, once rare, are rising rapidly

atrophic gastritis and intestinal metaplasia, and particularly to *cag+* strains of *H pylori*.¹⁸ In the future, reliable serological tests to detect abnormal gastric secretory function in conjunction with determining markers for *H pylori* strains should allow clinicians to identify those at high risk of developing cancer. (Current measurements of serum pepsinogens and gastrin, alone or in combination, are not clinically useful, and new approaches are needed before asymptomatic individuals can be screened.) The less common “diffuse type” of cancer is not associated with atrophic gastritis but has a greater familial tendency and presents earlier. In Japan identification of people with early presymptomatic gastric cancers by routine endoscopy over the age of 50 and the eradication of *H pylori* seem to have been effective in reducing development of subsequent cancers.¹⁹ Thus, even at a late stage in the oncogenic process, relevant pathophysiological steps may be blocked.

MALToma—Lymphoid proliferation is a common feature of *H pylori* colonisation. Occasionally, monoclonal expansion of gastric B cells results in malignant transformation and the development of high grade lymphoma. It is not clear, however, how often patients who have essentially benign lymphoid proliferation²⁰ are currently being labelled as having malignant disease. Although antimicrobial treatment is relatively safe, a goal for the future will be to differentiate true malignancy from monoclonal lymphoid proliferation.

Oesophageal disease—Further studies will confirm whether *H pylori* protects against gastro-oesophageal reflux disease, Barrett’s oesophagus, and adenocarcinomas of the gastric cardia and oesophagus and which bacterial genotypes are important. Assuming that some types of *H pylori* strains are protective, our whole approach to eradication treatment, which is becoming increasingly indiscriminate, will have to change dramatically. Risks as well as benefits will have to be estimated carefully in each patient for whom treatment is considered.

Non-ulcer dyspepsia—Despite the absence of firm recommendations, some doctors are now treating large numbers of patients with non-ulcer dyspepsia who are carrying *H pylori* with eradication treatment. Not surprisingly, results are mixed, which in part may reflect placebo effects. A priority for the future is therefore to stratify risk based on pathophysiological mechanisms or markers to define a subgroup of patients with dyspepsia related to *H pylori*, who stand to improve with treatment.

Asymptomatic carriage—Since eradicating *H pylori* may put people at increased risk of developing oesophageal disease, only in exceptional circumstances should asymptomatic individuals be treated. One group of patients who may benefit are those who have a first degree relative with gastric cancer.

Other clinical problems—Although an association of *H pylori* with the development of atherosclerotic heart disease has been reported, the attributable risk is small and could easily be due to unidentified confounding factors. People carrying *H pylori* may be slightly shorter (and possibly leaner) than their uncolonised counterparts. If true, this may be of epidemiologic interest, but it is unlikely to be clinically relevant.

Proposed temporal relations in upper gastrointestinal diseases

Time period	Predominant disease	Presumed association with <i>H pylori</i>
Ancient	Distal gastric cancer	<i>H pylori</i> acquisition in infancy
Pre-modern	Gastric ulcer	<i>H pylori</i> acquisition later
Modern	Duodenal ulcer	<i>H pylori</i> acquisition still later
Post-modern	Oesophageal disease	<i>H pylori</i> (<i>cag</i>) not acquired

Improved diagnosis and more rational treatment decisions

Deciding who should be assessed for the presence of *H pylori* is a contentious issue. However, remembering that (except for research) we should obtain information only if it can be used clinically, then the only people who should be tested at present are those with peptic ulcer disease, MALToma, or a strong family history of gastric cancer. None of the currently available diagnostic tests—biopsy techniques, urea breath tests, or serology—is completely reliable for *H pylori* because of heterogeneity in the density of bacterial colonisation and in host immune response. The use of two or more independent methods (such as serology and breath test) should bring sensitivity before treatment close to 100%. For evaluating the adequacy of treatment, however, the urea breath test seems to be optimal when done later than one month after the end of treatment. In the future, as we better understand the pathogenesis of the relevant diseases, diagnostic assays to assess differences between *H pylori* strains and host physiology will become routine.

Resistance to metronidazole and clarithromycin is increasing because of widespread use of these drugs (and related compounds) to treat other clinical conditions, and because failed treatment directed against *H pylori* leads to the emergence of (secondary) resistance. Current short term (7-10 days) quadruple treatments—including an acid reducing agent, a bismuth salt, and two antimicrobial drugs—are highly effective. After one or sometimes two treatments, it is possible to eliminate *H pylori* from nearly all patients because multi-drug resistance is still uncommon. The development of new treatments is therefore less crucial than determining which people to treat.

Disease prevention

If a suitable vaccine were available (research projects are ongoing) to prevent *H pylori* colonisation, would we increase or decrease the world’s disease burden? There

Technical terms

- **cagA**—The cytotoxin-association gene, which encodes a high molecular weight protein of unknown function, is a marker for the 38 kilobase *cag* island, which is present in *H pylori* strains that are more interactive with their hosts
- **Urea breath test**—Urea labelled with ¹⁴C or ¹³C is fed to a subject, and the carbon isotope is detected in exhaled CO₂. High values signify the presence of gastric urease activity, which is nearly always due to the presence of *H pylori*
- **vacA**—The gene encoding the vacuolating cytotoxin is present in all *H pylori* strains but is polymorphic. In Western populations particular alleles (such as s1a) are associated with increased risk of disease

may not be a single answer to this question; answers may vary with country, host genotype, and dietary factors. For example, a vaccination may be appropriate in parts of China where gastric cancer rates are high but not in the United States, where rates are low and the incidence of gastro-oesophageal reflux disease is increasing. In any case, with continuing socioeconomic development, *H pylori* colonisation is becoming less common. Monitoring trends in colonisation rates and upper gastrointestinal disease in differing populations should provide clues. Vaccination directed at preventing particular diseases rather than *H pylori* colonisation per se may be the way forward. The recent identification of the complete genomic sequence of one strain of *H pylori*²¹ will undoubtedly provide much information relevant to treatment, prevention, and diagnostics. Comparison of genetic sequences with those of "low virulence" strains should allow identification of the bacterial genetic bases of pathogenicity.

Are there individuals whom we should inoculate with *H pylori* to counter disease? And if so, which natural or attenuated strain, or combination of strains, should be used? We cannot answer these questions yet, but in the future it is conceivable that we will assess each infant and, based on factors such as its genotype, anticipated diet, and prevalence of particular diseases in its community, prescribe a strain (or strains) of *H pylori* to colonise that infant's stomach to maximise its chances of health. This may seem far-fetched, but it is in effect exactly what nature has done for us over millions of years; we are not randomly colonised, there has been selection for our normal flora. Particular organisms that increased the risk of diseases before the end of reproductive life have been selected against, while useful interactions have been selected for. The diseases we now associate with *H pylori* (or its absence) occur nearly exclusively after the reproductive period, so there is little natural selection for or against colonisation. Nevertheless, to best understand our future association with *H pylori*, we must be thinking in biological terms rather than merely in terms of patients' symptoms or of the hyperbole in drug advertisements and the lay press.

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Conflict of interest: MJB holds patents relating to *H pylori* genotypes, serology, and vaccines.

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A memorable patient

Piano player, pathologist, postmortem, postscript

Many years ago, while a singlehanded pathologist in a small prairie city, I played the piano in a small dance band. On this occasion the function was a private party for an older group, held in a hall with a wooden floor. The evening was well under way with lots of food and drink, a warm atmosphere, and the band playing a lively polka. Suddenly there was a dull thud, which could mean only the collapse of one of the dancers. The crowd slowly became quiet; the band one by one stopped playing.

A nurse present immediately started mouth to mouth resuscitation on the elderly man with no response, and since this was before the days of external cardiac massage, I felt obliged to do something. The kitchen was beside the dance floor and the

body was quickly dragged there while I shouted for a knife. A small kitchen knife was produced and with some difficulty I made the intercostal incision and was able to grasp the flaccid heart but was unable to produce any response. The next morning, on the coroner's order, I performed an autopsy and the extent and severity of the triple coronary artery disease confirmed the sequence of events.

The subsequent obituary in the local paper thanked me personally—the only occasion as a pathologist for 41 years, performing about six thousand autopsies, ever being thus appreciated.

James Hendry, retired pathologist, Nelson, British Columbia, Canada