Evidence based medicine and extradigestive manifestations of *Helicobacter pylori*

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Abstract

A putative pathogenetic role has been ascribed to Helicobacter pylori in several extradigestive diseases, including vascular (atherosclerosis and ischaemic heart disease, primary Raynaud phenomenon, primary headache), autoimmune (Sjögren's syndrome, Henoch-Schönlein purpura, autoimmune thyroiditis, idiopathic arrythmias, Parkinson's disease, nonarterial anterior optic ischemic neuropathy), and skin diseases (chronic idiopathic urticaria, rosacea, alopecia areata), sideropenic anemia, growth retardation, late menarche, extragastric MALT lymphoma, diabetes mellitus, hepatic encephalopathy, sudden infant death syndrome, and anorexia of aging. We examine critically the strength of the evidence linking these diseases to Helicobacter pylori, using ischaemic heart disease as an example of epidemiological techniques, and skin diseases as an example of treatment studies. By the standards of evidence-based medicine, studies have been often of low quality. The best evidence usually is not indicative of a role for Helicobacter pylori in these diseases. (Acta gastroenterol. belg., **2000**, 63, **388-392**).

Key words : Helicobacter pylori, evidence-based medicine, extradigestive, skin diseases, ischaemic heart disease, review, tutorial.

Introduction

Several partly overlapping waves can be described in the acceptance of Helicobacter pylori as a pathogen. The first wave involved the recognition of Helicobacter pylori as the aetiological agent of chronic active gastritis, without any practical consequences (1). During the second wave, the aetiological role of Helicobacter pylori in duodenal ulcer and later gastric ulcer was found (2). Helicobacter pylori eradication as an alternative for long term acid suppression in peptic ulcer disease became a textbook example of a 'paradigm shift' : the concept revolutionized the understanding of and the attitude toward 'peptic' ulcer disease. It took time however to replace the old paradigm of acid suppression, involving a highly interesting time frame of cognitive dissonance during which many people familiar with the Helicobacter pylori knowledge base agreed on the benefits of Helicobacter pylori eradication in peptic ulcer disease but failed to apply this knowledge in practice. The third wave concerns the role of Helicobacter pylori as a class I carcinogen (3) ; this wave is still ongoing, since there is not yet a firm definitive attitude towards Helicobacter pylori eradication as a public health measure for avoiding gastric cancer. The fourth wave is now picking up, describing extradigestive manifestations of Helicobacter pylori.

These four time frames correspond to different levels of certitude concerning the role of Helicobacter pylori in these pathologies and the necessity of Helicobacter pylori treatment, as evidenced for instance in the Maastricht guidelines (4), in which Helicobacter pylori eradication was either strongly recommended, advisable or'uncertain'. Supporting evidence was qualified as unequivocal, supportive, or 'equivocal'. Chronic active gastritis is absolutely linked to Helicobacter pylori, but is not an indication for diagnosis and treatment per se. Helicobacter pylori eradication was judged strongly recommended in gastritis with severe abnormalities, based on supportive evidence. Helicobacter pylori eradication is strongly recommended in peptic ulcer disease, based on evidendence deemed 'unequivocal'. Helicobacter pylori eradication was likewise judged strongly recommended in Low grade gastric MALT lymphoma, based on unequivocal evidence. The situation is completely different for Helicobacter pylori and gastric carcinoma : Helicobacter pylori eradication for prevention of gastric cancer in the absence of risk factors is considered as an uncertain indication, supported by equivocal evidence ; Helicobacter pylori eradication is judged 'advisable' for family history of gastric cancer, based on equivocal evidence ; it is strongly recommended following endoscopic resection for early gastric cancer, based on supportive evidence. Extra-alimentary tract disease finally was judged an uncertain indication for Helicobacter pylori eradication, based on equivocal evidence.

Recently, several excellent reviews (5,6,7) have been dedicated to exploring the role of Helicobacter pylori in extradigestive manifestations. We will build on this knowledge base and add some new data that appeared in the literature since the publication of these reviews. We will not discuss the involvement of Helicobacter species in lower digestive tract disease or hepato-biliary disease, and we will concentrate on the quality and type of evidence linking Helicobacter pylori to extradigestive diseases, as compared with chronic gastritis, peptic ulcer disease, and gastric cancer.

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Diseases in which a role has been suspected for Helicobacterpylori

In several nondigestive diseases, a putative pathogenetic role has been ascribed to Helicobacter pylori. These allegedly Helicobacter pylori-related diseases include (5,6,7) vascular (atherosclerosis and ischaemic heart disease, primary Raynaud phenomenon, primary headache), autoimmune (Sjögren's syndrome, Henoch-Schonlein purpura, autoimmune thyroiditis, idiopathic arrythmias, Parkinson's disease, nonarterial anterior optic ischemic neuropathy), and skin diseases (chronic idiopathic urticaria, rosacea, alopecia areata), as well as sideropenic anemia, growth retardation, late menarche, extragastric MALT lymphoma, diabetes mellitus, hepatic encephalopathy, sudden infant death syndrome, and anorexia of aging. These associations have usually been based on finding a higher prevalence of Helicobacter pylori infection in cases than controls (epidemiological studies) ; sometimes the observed disease disappeared or improved after Helicobacter pylori eradication (treatment studies) (8). Treatment studies are a quick way for determining the role of Helicobacter pylori in an acute disease ; epidemiological studies are needed before treatment studies can start in chronic diseases. As an example of epidemiological investigations, we will examine more closely the story of Hp and ischaemic heart disease ; for treatment studies, skin diseases are a good example.

Epidemiological investigations : the case of Helicobacter pylori and ischaemic heart disease

Mendall *et al.* (9) were the first to describe an association between Helicobacter pylori and ischaemic heart disease. They found a 59% seroprevalence of Helicobacter pylori in 111 patients with coronary heart disease vs. 39% in 74 controls (odds ratio 2.28, p = 0.007).

The first step in interpreting these data is to rule out confounding parameters. After adjustment for age, cardiovascular risk factors, and socio-economic status, the odds ratio for ischaemic heart disease in the presence of Helicobacter pylori was 2.15, p = 0.3.

This stimulated the interest in the possible link between ischaemic heart disease, atherosclerosis, stroke, and Helicobacter pylori. Helped by a strong foundation of epidemiology in cardiovascular research, several epidemiological case-control studies with contrasting results were published.

The techniques of meta-analysis allow to test for the homogeneity of the results between studies, and to estimate a pooled result of the odds ratio.

In a meta-analysis from 1997, covering 4 prospective studies, 4 studies with population controls, and 12 studies with other controls, Danesh *et al.* (10) concluded there was no evidence for a causal association between Helicobacter pylori and IHD. Strachan (11) separately reviewed 6 published case — control and survey studies and 7 abstracts. The abstracts were highly inconsistent ; published studies on the other hand were consistent and showed a pooled odds ratio of 1.4 with confidence limits 1.1-1.8, indicating a possible weak association between Helicobacter pylori and IHD.

In incident case control studies, patients with a disease are compared to controls from the general population. In nested case-control studies, a large cohort of people is included at base-line, during which several measurements are made and blood is stored. This cohort is then followed over years, and cases of the disease are identified. Within the cohort, disease-free controls are chosen who are matched as well as possible with the cases, based on the measurements performed at baseline. For Helicobacter pylori studies, blood is then thawed and Helicobacter pylori serology performed. Prospective studies, in the form of nested case-control studies, are more powerful than incident case-control studies, because some biases are avoided (12) : the controls are internal to the study population ; any influence of the disease process itself on the factors being studied can be avoided ; large prospective studies should be less subject to publication bias. Moreover, they introduce the important notion of temporality : the studied parameter is shown to precede the disease in time.

In a review of prospective studies, Danesh (12) reviewed 5 well adjusted (for age, sex, smoking, standard vascular risk factors, and 3 out of 5 for social class) studies totalling 1727 patients. The pooled odds ratio of Helicobacter pylori for ischaemic heart disease was 1.1 with confidence limits between 0.9 and 1.4 (ns). Prospective studies therefore do not support any role for Helicobacter pylori in ischaemic heart disease.

Another way of improving the results of case-control studies in the general population is to try to diminish background noise in the control patients. Since the prevalence of Helicobacter pylori increases with age, the Helicobacter pylori prevalence in the control group will be lower in younger people. Looking at disease in younger patients (and therefore having younger controls) might uncover disease associations that get buried in background noise when considering the whole population. This is for instance the case for gastric cancer, where the oods ratio for Helicobacter pylori increases sharply with decreasing age (13). Danesh performed a case-control and a sibling pairs study addressing the issue of Helicobacter pylori and early onset myocardial infarction (14). 42% of 1122 cases with early onset myocardial infarction (age 30-49) were seropositive for Helicobacter pylori, as compared with 24% of the age and sex matched controls, giving an odds ratio of 2.28 (1.80-2.90). This odds ratio fell to 1.87 (1.42-2.47) after adjustment for smoking and socioeconomic status, and to 1.75 (1.29-2.36) after additional adjustments for blood lipids concentrations and obesity. Among siblings,

158 of 510 were discordant for Helicobacter pylori ; among these, 91 cases and 67 controls were seropositive for Helicobacter pylori, yielding an odds ratio of 1.33 (0.86-2.05). The evidence for a role of Helicobacter pylori in early- onset ischaemic heart disease therefore is weak at best.

In spite of enthusiastic first results, subsequent studies thus show only a possible weak association between Helicobacter pylori and ischaemic heart disease, if any exists at all. The studies show the extreme importance of the word 'control' in the expression 'case-control' : when more factors are controlled for, the residual relationship becomes weaker at every step. Helicobacter pylori being ubiquitous bacteria, the prevalence of which is related to age and socio-economic factors, spurious correlations are easily found. This cuts straight to the heart of epidemiological studies : when one finds an association between Helicobacter pylori and some disease, it can be hard to decide whether Helicobacter pylori is the cause of this disease, or whether Helicobacter pylori is just an indicator, i.e. the disease is more frequent in people who also happen to be Helicobacter pylori positive, because some other factor is increasing the risk for Helicobacter pylori and for the observed disease, such as socio-economic status for ischaemic heart disease.

Epidemiologists have developed criteria for increasing the likelihood that an observed association is indeed causal. The best known of these are the Bradford Hill criteria (15), which examine (1) temporality (was Helicobacter pylori present before the disease started) ; (2) is there any doseresponse relationship (this is difficult to test with Helicobacter pylori ; the closest correlate would be density of Helicobacter pylori on gastric biopsies or Helicobacter pylori serotiter) ; (3) consistency (are the results of different studies concordant in meta-analysis) (4) strength of association (pooled odds ratio in meta-analysis) (5) analogy (are there other biological phenomena known involving analogous mechanisms) ; (6) specificity (is any disease specific for Helicobacter pylori) ; (7) biological plausibility (can one think of reasonable hypotheses explaining the observed association) ; (8) experiment (are there any in vitro, animal, or human experiments supporting the observed association). These criteria are examined in table 1, as adapted from Leontiadis *et al.* (7).

Temporality was negative in the nested case-control studies for ischaemic heart disease, and is untested for other extradigestive diseases ; it is present for chronic gastritis, peptic ulcer disease, and in the nested case-control studies for gastric cancer. A dose - response relationship was not tested for in ischaemic heart disease and other extradigestive diseases ; the activity of chronic gastritis is related to bacterial density ; bacterial density is higher in peptic ulcer disease patients than in Non-ulcer dyspepsia patients ; there is a positive relationship between Helicobacter pylori serotiter and risk of gastric cancer is some of the nested case-control studies on gastric cancer.

The association is not consistent for ischaemic heart disease or other extradigestive diseases ; it is consistent for chronic active gastritis and peptic ulcer disease ; long term nested case-control studies for Helicobacter pylori and gastric cancer are positive but short-term are not.

The association is weak at most for ischaemic heart disease and other extradigestive diseases ; it is strong for chronic active gastritis, peptic ulcer disease, and gastric cancer.

As for analogy, other infectious agents have been considered in ischaemic heart disease, such as dental disease, Chlamydia pneumoniae, cytomegalovirus and herpesviruses (12), and atherosclerosis has been considered an inflammatory disease (16). Nevertheless, at most weak associations have been found between these infectious diseases and ischaemic heart disease (12). No analogous disease are found for extradigestive diseases. The analogy for chronic gastritis is of course every infectious

Table I

	Ischaemic Heart Disease	Other extra-digestive diseases	Chronic active gastritis	Peptic ulcer disease	Gastric non-cardia cancer
Temporality	Negative	Untested	Yes	Yes	Yes
Dose-response	Not tested	Not tested	Yes	Yes	Yes
Consistency	No	No or not tested	Yes	Yes	Yes in long-term nested case-control studies
Strength of the association	Weak or absent	Weak or absent	Strong	Strong	Strong
Analogy	Infections, inflammation	No	Yes	No	Yes
Specificity	No	No	Yes	No	No
Biological plausibility	Weak	Weak	Yes	Yes	Yes
Experimental data	No	No	Human yes, animal yes	Human no, animal yes	Human no, animal yes

Adapted from Leontiadis *et al.* (7).

disease that causes inflammation ; there is no analogy for peptic ulcer disease ; for gastric cancer, analogies are other infectious agent-related cancers such as hepatocellular carcinoma and hepatitis.

No Helicobacter pylori related disease is specific except for chronic active gastritis.

Biological plausibility is weak for extradigestive diseases, it is strong for chronic active gastritis, peptic ulcer disease and gastric cancer.

Experimental data are absent in extradigestive diseases ; experimental infection with Helicobacter pylori causes chronic active gastritis in humans and in animals ; there is no documented case of peptic ulcer or gastric cancer in any human self-inoculation experiment (although the development of atrophic gastritis, a known preneoplastic lesion, has been documented in several cases of accidental Helicobacter pylori inoculation), but Helicobacter infection causes peptic ulcers and gastric cancer in the ferret and the mongolian gerbil.

High quality epidemiological studies have only been reported for ischaemic heart disease and Helicobacter pylori, and these show at most a weak association. In the other extradigestive diseases, 'epidemiological' studies have severe deficiencies, especially for lack of adequate controls and small size (7).

If anything, epidemiological studies are certainly not in favor of an important role for Helicobacter pylori in any of the allegedly Helicobacter pylori-related extradigestive diseases.

Treatment studies : the case of Helicobacter pylori and skin diseases

So how about treatment studies ? The only controlled studies of Helicobacter pylori eradication in extradigestive diseases have been performed in dermatology.

In an uncontrolled study (17), Rebora *et al.* found that 85% of 31 patients with rosacea had evidence of Helicobacter pylori infection, and in an uncontrolled study from Ireland (18), Helicobacter pylori seroprevalence was 95% in rosacea patients. In a controlled study (19), Schneider found a Helicobacter pylori seroprevalence of 49% in 94 patients, compared with 53% in 32 patients with dermatitis, and in another controlled study, Sharma *et al.* (20) found a Helicobacter pylori seroprevalence of 27% in 45 rosacea patients as compared to 35% in age-adjusted controls.

Kolibasova *et al.* (21) reported one patient in whom rosacea cleared after Helicobacter pylori eradication.

Bamford *et al.* (22) performed a randomised controlled trial of Helicobacter pylori eradication therapy for rosacea. 50/320 rosacea patients had a positive urea breath test, 44 were included in the study : 22 patients received placebo, and 22 received 14 days of omeprazole 40 mg/d and clarithromycin 3 × 500 mg/d ; 20 of these patients completed the study. Helicobacter pylori eradication was achieved in 15/20 patients (as expected with this treatment). An improvement in the skin lesions was observed in both patients on active treatment and placebo ; lessening of rosacea for Helicobacter pylori treated patients was not better than for the placebo-treated patients. Although the study population is small and the treatment suboptimal to current standards, this study suggests that Helicobacter pylori eradication does not improve rosacea.

A similar story can be told for chronic urticaria (7) : uncontrolled small studies show a high prevalence of Helicobacter pylori ; uncontrolled Helicobacter pylori treatment is associated with improvement of urticaria.

Schnyder *et al.* (23) performed a double blind placebo controlled cross-over study in 12 Helicobacter pylori positive patients out of 46 evaluated, using amoxycillin and lansoprazole. This suboptimal treatment scheme resulted in Helicobacter pylori eradication in only 3 patients, in whom urticaria improved in only 1 patient. Urticaria improved spontaneously within 6 months in 41% of untreated patients.

Valsecchi *et al.* (24) found a marginally higher Helicobacter pylori prevalence in 62.4% of urticaria cases versus 49.4% of controls. Complete remission of urticaria was observed in 3/31 patients who received Helicobacter pylori eradication therapy and in 1/34 controls (ns).

Treatment studies for Helicobacter pylori in extradigestive diseases therefore are scarce, and suffer from major deficiencies : they have quite small study populations and treatment is suboptimal. The few studies that are there suggest that Helicobacter pylori eradication does not influence the examined extradigestive disease.

Evidence-based medicine and extradigestive manifestations of Helicobacter pylori

Meta-analysis of randomised controlled trials of reasonable size is the cornerstone of evidence-based medicine. None of the 3 negative controlled trials in Helicobacter pylori and skin diseases live up to these standards. Nevertheless, they show that even small sized trials with suboptimal treatment "regimens are more interesting than uncontrolled series and case reports. Sadly, these 3 trials are the only randomised trials that have been reported as yet in any of the alleged Helicobacter pylori related extradigestive diseases. There is therefore no good indication for treating Helicobacter pylori in extradigestive diseases.

When randomized controlled trials are not available, informed opinions can be formed based on circumstantial evidendence from epidemiological data. A classical example is the general acceptance of Helicobacter pylori as an important risk factor for gastric adenocarcinoma, although no randomized controlled trial shows that Helicobacter pylori eradication will definitely prevent gastric cancer (no randomized controlled trial has been performed which examined this — absence of evidence

is not evidence of absence). Circumstantial evidence does however not replace a good randomized controlled trial. Using fresh fruits and vegetables is one of the strongest predictors for a negative risk of many types of cancer ; nevertheless, well conducted intervention studies with vitamins (25 nejm 1993) or fibers (26,27) were unable to detect any effect of these interventions, showing that even the best hypotheses with consistent supportive data can be shattered by a true-life experiment.

In the case of extradigestive manifestations of Helicobacter pylori, many studies examining a possible causal relationship have been uncontrolled or inadequately controlled. Studies have often failed to control for socio-economic status. Studies of treating H pylori infection in patients with these disorders have been poorly designed and inappropriately controlled, and therefore add little to the evidence base (7 leontiadis).

By the standards of evidence-based medicine, Helicobacter pylori eradication is not indicated in any of the cases of allegedly Helicobacter pylori related extradigestive diseases as a treatment for these diseases, and the best current circumstantial evidence pleads quite strongly against a role for Helicobacter pylori in any of these diseases.

One may still choose to eradicate Helicobacter pylori in these patients, but it should be clear that this attitude will be chosen for reasons other than treatment of these diseases : one may wish to protect the patient from peptic ulcer disease or gastric cancer (primary prevention in both these indications is unproven and speculative, although most helicobacteriologists would expect a positive result if ever a randomized controlled trial of sufficient scale — patient numbers and time span — would be performed ; again, absence of evidence is not evidence of absence), or one may wish to eradicate all Helicobacter pyloris from the earth's surface, as was possible with smallpox (although an infectious disease never has been eradicated with antibiotics, it has until now always necessitated a vaccine).

Research on the role of Helicobacter pylori in extradigestive diseases may be continued, but should adhere to higher standards than has been the case until now. Case-control studies should include more patients, and select controls more carefully. Nested case-control studies and case control studies in younger sujects should be encouraged. Treatment studies should be prospective double blind randomised controlled trials with enough patients. Below-standards research should not be performed, and its results should not be published.

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