Extragastroduodenal conditions associated with *Helicobacter pylori* infection

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Helicobacter pylori **is a Gram-negative bacterium that is considered a causative agent of peptic ulcer disease, gastric lymphoma, and gastric carcinoma.** ***Helicobacter pylori*** **triggers an intense leucocyte infiltration of the gastric submucosa, an action which is mediated by pro-inflammatory cytokines. This pathogenetic mechanism is common to many other diseases and consequently,** ***Helicobacter pylori*** **seroprevalence has also been investigated in other diseases. It is now known that** ***Helicobacter pylori*** **seropositivity is associated with various cardiovascular, respiratory, extragastroduodenal digestive, neurological, dermatological, autoimmune, and growth disorders. Although the precise role of** ***Helicobacter pylori*** **is unknown in these diseases, the organism can be eradicated using simple and reliable drug regimens. The conditions associated with** ***Helicobacter pylori*** **seropositivity are highlighted in this article.**

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Introduction

Helicobacter pylori is a micro-aerophilic, Gram-negative, spiral-shaped bacterium and its discovery revolutionised approaches to the pathogenesis and treatment of peptic ulcer disease.[1] The organism is causally related to chronic active gastritis[2]; peptic ulcer disease[2]; primary low-grade (B-cell) gastric lymphoma[3]; and gastric carcinoma.[4] Recent epidemiological studies have revealed an association between *H pylori* seroprevalence and increasing age,[5] lower socio-economic status,[6] and crowding at home.[7] A high *H pylori* seroprevalence has also been reported in patients with a range of systemic diseases including ischaemic heart disease. This is particularly important, as *H pylori* seropositivity can be as high as 60% in Hong Kong, even in apparently healthy adults.[8] If *H pylori* does have such pathogenic potential, then its impact on health care, disease patterns, and the treatment of all the related diseases would be colossal. Most general readers are confronted with and sometimes frustrated by an ever-expanding list of conditions associated with *H pylori* seropositivity. Accordingly, this article has been compiled to highlight some of the known associations and the scientific basis of *H pylori* infections.

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The pathogenesis of *H pylori* infection

Helicobacter pylori is a versatile organism and produces a range of toxins that are detrimental to gastric mucosa both in vivo and in vitro.[9] These toxic factors include urease, phospholipase, alcohol dehydrogenase, vacuolating cytotoxin, haemolysin, platelet activating factor, and mucolytic factor.[9] While the toxins are undoubtedly harmful to the stomach and duodenum, they also interact with other tissues in the body. *Helicobacter pylori* has been shown to adhere to several cell lines derived from different organs of the body.[10] The effects of these toxins and their interactions with gastroduodenal and other tissues are outlined in the Table.[11-18]

The presence of *H pylori* in the gastric mucosa is almost always associated with mucosal inflammation due to infiltration by neutrophils and monocytes.[19,20] Harmful enzymes such as urease, catalase, protease, lipase, and phospholipase are produced by *H pylori* and may be involved in the pathogenesis of gastric inflammation.[17,21-25] The levels of tumour necrosis factor (TNF) alpha, interleukin (IL)-1b, and IL-8 are all raised in the gastric mucosa of patients with *H pylori* infection compared with those who are not infected.[26] Interleukin-1b is implicated in the recruit-

Table. *H pylori* exotoxins that potentially have activity at extragastroduodenal sites

Factor produced	Source	Toxic effect/s	Reference
Ammonia	*H pylori* urease	Inhibition of protein degradation and vacuolation of lysosomes	11
Lysolecithin	*H pylori* phosopholipases	Cytotoxic compound leading to ulceration	12
Acetaldehyde	*H pylori* alcohol dehydrogenase	Denaturation of proteins and induction of lipid peroxidation	13
Vacuolating cytotoxin	50% of *H pylori* organisms	Vacuolation of eukaryotic cells via unknown mechanisms	14
Haemolysin	*H pylori* phospholipase?	Haemolysis	15
Platelet activating factor	Unknown	Potent inflammatory mediator in various organs	16
Mucolytic factor	Unknown	Degradation of mucin	17
Lipopolysaccharide	*H pylori* cell wall	Low biological activity but could inhibit mucin glycosylation	18

ment of circulating neutrophils to sites of inflammation,[27] is a chemoattractant to neutrophils, and stimulates induction of IL-8 in vivo.[28] Interleukin-8 is synthesised by many cells after stimulation by IL-1b, TNF-α, or endotoxin and is the most potent chemoattractant known; it also induces the release of proteases from neutrophils.[29] *Helicobacter pylori* causes the release of growth-regulated chemokines, macrophage inflammatory proteins, and monocyte chemotactic activating factor, all of which are involved in the generation of the intense inflammatory reaction that occurs in gastric mucosa.[30]

H pylori infection and associated disorders

An increasing number of extragastroduodenal conditions have been related to *H pylori* infection over the past decade. The vast majority, if not all, of the studies have however, employed serological surveillance rather than isolation of *H pylori* from the target disease site. This limitation is almost certainly due to the difficulty in culturing *H pylori* as well as the remoteness of some of the target sites, such as the airway and coronary arteries. Fortunately, serological testing to indirectly detect *H pylori* is quick, relatively cheap, specific, and can be performed using commercially available test kits.

Cardiovascular disorders

At least five studies have investigated the relationship between *H pylori* seroprevalence and the risk of coronary heart disease.[31-35] However, whether or not *H pylori* infection is associated with an increased risk for the development of coronary heart disease remains to be determined. The uncertainty is because these studies have conflicting results, even when the differences in their diagnostic criteria of coronary heart disease have been accounted for. The largest of the surveys was a case-control study in which controls showed significantly lower *H pylori* seropositivity rates than did men who had had a myocardial infarction (57% and 70%, respectively; odds ratio [OR]=1.77, P=0.03).[32] But the association between *H pylori* seropositivity and myocardial infarction became insignificant (P=0.40) after adjusting for social class, residence in high-risk areas, cigarette smoking, high systolic and diastolic blood pressure, and a lower 1-second forced expiratory volume.[32]

Although there is still no definitive evidence to link *H pylori* infection with coronary heart disease, various findings support this association. For example, *H pylori* infection has been shown to be associated with an increase in the level of fibrinogen (after adjusting for confounding risk factors including age and smoking).[36] In addition, *H pylori* infection is also associated with a deterioration in lipid profiles, an event which could promote atherosclerosis.[35] Other disease mechanisms that have been suggested include the reduction in the level of antioxidants and the promotion of production of pro-inflammatory mediators.[37]

Respiratory disorders

Bronchiectasis is a chronic infective and inflammatory disease of the tracheobronchial tree. Affected patients suffer from recurrent sputum production, haemoptysis, and bouts of exacerbations. Although many known causes of bronchiectasis have been identified, more than 60% of cases have an unknown cause.[8] *Helicobacter pylori* has been recently identified in the tracheobronchial aspirates of mechanically ventilated patients and the possibility that *H pylori* infection might

cause ventilator-associated pneumonia has been raised.[38]

There are interesting similarities between the pathogenesis of bronchiectasis and ulcers. Intense infiltration of the airway or gastric mucosa with neutrophils and T lymphocytes,[20,39] (mediated by cytokines, especially IL-8, TNF-α, and IL-1b)[40] occurs in both conditions. Respiratory pathogens such as *Haemophilus influenzae* and *Pseudomonas aeruginosa* persist in the tracheobronchial tree[41]; similarly, *H pylori* can persist within the gastric mucosa for decades.[42] These organisms cause ultrastructural damage to their target mucosal cells, such as vacuolation and extrusion from the mucosal surface.[43-45]

Our group has recently reported a high incidence of *H pylori* seropositivity in patients with bronchiectasis (76.0%) compared with healthy controls (54.3%; P=0.001) and patients with tuberculosis (52.9%; P=0.0001), even after accounting for age, social class, and household crowdedness.[8] The increase in *H pylori* seroprevalence appeared to correlate with disease activity, because the *H pylori* immunoglobulin (Ig) G antibody level correlated with sputum production by the patients with bronchiectasis. The similarities between the disease process in bronchiectasis and ulceration might be due to a chronic inflammatory disease or bacteria-induced tissue damage. It is also possible that aspiration of *H pylori* or its toxins into the respiratory tract could occur, particularly given the prevalence of gastro-oesophageal reflux in patients with bronchiectasis.[14]

Although asthma is also an inflammatory disease of the airways and its pathogenesis involves similar pro-inflammatory mediators as are present in bronchiectasis and ulceration, a recent study of asthmatic patients in Hong Kong showed no association between asthma and *H pylori* seropositivity.[46]

Extragastroduodenal digestive disorders

There have been extensive investigations to find *H pylori* seropositivity in other extragastroduodenal digestive disorders, but despite the volume of work, proven associations are still few. An association has been shown between *H pylori* seropositivity and the development of hepatic encephalopathy in cirrhotic patients.[47] Another study showed that patients with pancreatic carcinoma had a *H pylori* seropositivity of 65% compared with the controls' rate of 45% (OR=2.1).[48] However, this study has been partially discredited because of the lack of controlled data to eliminate the effects of confounding factors, which are known to affect *H pylori* seropositivity.

Other studies have yielded negative results for associating *H pylori* seropositivity with a disease state. Examples of such diseases are recurrent aphthous stomatitis and other oral disorders,[49] inflammatory bowel disease,[50] portal hypertensive gastropathy,[51] coeliac disease,[52] cirrhosis,[53] and Barrett's oesophagitis.[54]

Neurological disorders

Similar to coronary heart disease, stroke is predominantly related to atherosclerosis of the arteries. Consequently, investigators have studied the relationship between *H pylori* infection and cerebrovascular disease. There are at least two published and well-designed studies that depict an association between *H pylori* seropositivity and cerebrovascular disease.[32,55] The more recent and larger study showed *H pylori* seropositivity to be 58.8%, while that of the control group was 44.5% (P=0.01). The odds ratio for cerebrovascular disease associated with *H pylori* seropositivity of 1.78 was significant, even after adjusting for confounding factors such as age and social class.[55]

Growth disorders

Studies have also suggested that an association exists between small stature and *H pylori* seropositivity.[6,56] One study followed the growth (in height) from age 7 to 11 years in 554 schoolchildren and found that 11% of them showed evidence of *H pylori* seropositivity by 11 years of age; these children also had significantly lower heights, even after adjustments had been made for housing, parental social class, and school catchment area.[6] The growth reduction was largely confined to girls, among whom height correlated with salivary IgG values (P=0.05).[6] A similar study performed in Denmark has also shown that *H pylori* seropositivity is associated with late menarche.[57] The causal linkage of growth retardation to the presence of inflammatory mediators in those children who are *H pylori*–seropositive is purely speculative and remains to be proven. Further work is clearly necessary to confirm this finding in other ethnic groups and to determine the underlying mechanism by which growth retardation occurs during *H pylori* infection.

Dermatological and autoimmune disorders

Helicobacter pylori seropositivity has been associated with the presence of rosacea, urticaria, and alopecia aerata.[58,59] *Helicobacter pylori* seropositivity in Henoch-Schönlein purpura has also been reported.[60] Although these studies are generally small (eg in the rosacea study, there were only 31 subjects) and do not have control group data for comparison, they are particularly interesting because eradication of *H pylori* resulted in improvement of rosacea,[58] urticaria,[59] and

Henoch-Schönlein purpura.[60] Although these data and claims of efficacy need to be evaluated by proper controlled clinical trials, they provide very important insights into these still largely idiopathic diseases.

There are also other sporadic case reports or small series which show an association between *H pylori* seropositivity and a number of autoimmune disorders including atrophic thyroiditis,[61] Sjögren's syndrome,[62] and idiopathic thrombocytopenia.[63] Similar to the study of bronchiectasis described above,[8,40] a study involving 59 patients with atrophic thyroiditis[61] showed that disease activity correlated with the level of anti–*H pylori* IgG antibodies present. This suggests a role for *H pylori* in the pathogenesis of atrophic thyroiditis rather than a mere serological association.

Other associated diseases

A handful of small studies suggest an association between *H pylori* seropositivity and other diseases. These include the increased seroprevalence of *H pylori* found in individuals affected by Raynaud's phenomenon and the fact that eradication therapy improves the duration and frequency of clinical attacks that patients experience.[64] An association between 143 cases of diabetes mellitus (45 of them insulin- dependent) and *H pylori* seropositivity has been reported; this observation is independent of age, social class, and antibiotic treatment.[65] In addition, there is also an association between *H pylori* seropositivity and headache, including migraine.[64,66] Although these studies are indicative of a possible association, the small sample size involved and lack of adjustment for confounding factors makes it difficult to interpret the data.

Conclusion

The list of diseases that are associated with *H pylori* seropositivity is expanding rapidly but has to be interpreted with caution, as controlled data are not always available. This is compounded by the difficulty in excluding other confounding factors such as age, social class, household crowdedness, residence in a developing country (where *H pylori* infection is pandemic), other associated diseases, and yet still unknown factors. The pandemic nature of *H pylori* seroprevalence suggests that even if the organism plays a role in the pathogenesis of so many diseases, it might only be acting as a cofactor. Basic scientific research to determine whether or not there is conclusive evidence to link the pathogenesis of diseases with the presence of *H pylori* should be performed. Clinicians and researchers will and should undoubtedly pursue these exciting developments in basic and clinical research.

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