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• REVIEW •

Helicobacter pylori infection and respiratory diseases: a review

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Abstract

In the past few years, a variety of extradigestive disorders, including cardiovascular, skin, rheumatic and liver diseases, have been associated with *Helicobacter pylori* (*H. pylori*) infection. The activation of inflammatory mediators by *H. pylori* seems to be the pathogenetic mechanism underlying the observed associations. The present review summarizes the current literature, including our own studies, concerning the association between *H. pylori* infection and respiratory diseases.

A small number of epidemiological and serologic, case-control studies suggest that *H. pylori* infection may be associated with the development of chronic bronchitis. A frequent coexistence of pulmonary tuberculosis and *H. pylori* infection has also been found. Moreover, recent studies have shown an increased *H. pylori* seroprevalence in patients with bronchiectasis and in those with lung cancer. On the other hand, bronchial asthma seems not to be related with *H. pylori* infection.

All associations between *H. pylori* infection and respiratory diseases are primarily based on case-control studies, concerning relatively small numbers of patients. Moreover, there is a lack of studies focused on the pathogenetic link between respiratory diseases and *H. pylori* infection. Therefore, we believe that larger studies should be undertaken to confirm the observed results and to clarify the underlying pathogenetic mechanisms.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a slow-growing, microaerophilic, gram-negative bacterium, whose most striking biochemical characteristic is the abundant production of urease. This bacterium colonizes gastric mucosa and elicits both inflammatory and immune lifelong responses, with release of various bacterial and host-dependent cytotoxic substances[1]. Pathological studies and extensive clinical trials, carried out in the past few years, have proved the causative role of *H. pylori* in the development of chronic gastritis[2] and peptic ulcer disease[3]. It seems that this bacterium is also causally related to low-grade B-cell lymphoma of gastric mucosa-associated-lymphoid-tissue (MALT-lymphoma)[4]. Moreover, *H. pylori* infection has been established as a risk factor for the development of both diffuse and intestinal types of gastric cancer[5].

Recent studies suggest an epidemiological association between *H. pylori* infection and several extragastroduodenal pathologies, including cardiovascular, skin, rheumatic and liver diseases (Table 1)[6,7]. Unfortunately, such epidemiological studies are influenced by a wide variety of confounding factors, i.e. socioeconomic status, time of acquisition of the infection, presence of different bacterial strains and previous antibiotic therapy. However, according to many authors, the observed associations might be true and explained by a role of *H. pylori* infection in the pathogenesis of certain extradigestive disorders. It is well known that *H. pylori* colonization of the gastric mucosa stimulates the release of various proinflammatory substances, such as cytokines, eicosanoids and proteins of the acute phase[8]. Moreover, a cross mimicry between bacterial and host antigens exists in *H. pylori* infected patients[9]. Therefore, a pathogenetic link between *H. pylori* infection and diseases characterized by activation of inflammatory mediators and/or induction of autoimmunity might exist.

Chronic inflammation and increased immune response have been observed in a variety of respiratory diseases, including chronic bronchitis[10,11] and bronchiectasis[12]. Moreover, both chronic obstructive pulmonary disease[13,14] and pulmonary tuberculosis[15] are more prevalent in peptic ulcer patients than in the general population. Based on these facts, many recent studies have focused on the potential association between *H. pylori* infection and various respiratory disorders. Table 2 summarizes those respiratory diseases whose relation with *H. pylori* infection has been studied in the literature.

The aim of the present report is to provide a critical review of the current literature, including our own studies, as regards the association between *H. pylori* infection and respiratory diseases.

Table 1[6,7] Extradigestive diseases associated with *H. pylori* infection

Vascular diseases
Ischaemic heart disease
Primary Raynaud's phenomenon
Primary headache
Skin diseases
Idiopathic chronic urticaria
Rosacea
Alopecia areata
Autoimmune diseases
Sjogren's syndrome
Autoimmune thyroiditis
Autoimmune thrombocytopenia
Schoenlein-Henoch purpura
Other diseases
Liver cirrhosis
Growth retardation
Chronic idiopathic sideropenia
Sudden infant death
Diabetes mellitus

Table 2 Respiratory diseases studied for a relatioship with *H. pylori* infection

Chronic bronchitis
Pulmonary tuberculosis
Bronchiectasis
Lung cancer
Bronchial asthma

HELICOBACTER PYLORI INFECTION AND CHRONIC BRONCHITIS

Chronic bronchitis is a pulmonary disease characterized by, primarily irreversible, airflow obstruction due to the chronic inflammation of the small airways. The presence of airflow obstruction that is not fully reversible is confirmed by spirometry (postbronchodilator FEV1<80 % of the predicted value, in combination with an FEV1/FVC<70 %). Although its true prevalence remains unknown, it is estimated that approximately 12.5 million persons in the United States suffer from chronic bronchitis[16].

Chronic bronchitis had been associated with gastroduodenal ulcer many years before the identification of *H. pylori* infection as a cause of peptic ulcer disease. Three epidemiological studies, carried out between 1968 and 1986, showed that the prevalence of chronic bronchitis in peptic ulcer patients was increased two-to-three fold compared with that in ulcer-free controls[13,14,17]. Moreover, a follow-up study demonstrated that chronic bronchitis was a major cause of death among patients with peptic ulcer disease[18].

The reported association between these two diseases was originally attributed to the known role of cigarette smoking as an independent factor in both ulcerogenesis and development of chronic bronchitis. However, in 1998, Gaseli and colleagues carried out a prospective pilot study in a sample of 60 Italian patients with chronic bronchitis and found an increased seroprevalence of *H. pylori* infection compared to that detected in 69 healthy controls (81.6 % versus 57.9 % respectively, P=0.008). In this study, the odds ratio for chronic bronchitis in the presence of *H. pylori* infection, calculated after adjustment for age and social status, was 3.4[19]. These results suggested, for the first time, that *H. pylori* infection per se might be related to an increased risk of developing chronic bronchitis. Two years later, a large epidemiological study in 3608 Danish adults showed that chronic bronchitis might be more prevalent in *H. pylori* IgG seropositive women than in uninfected ones (odds ratio 1.6, with a 95 % confidence interval of 1.1-2.5)[20]. In order to further investigate the reported association between *H. pylori* infection and chronic bronchitis, we recently performed a case-control study in a cohort of 144 Greek patients with chronic bronchitis and 120 control subjects. Our results were in accordance with those of Gaselli and associates, as we also found that *H. pylori* seropositivity in patients was significantly higher than that in controls (83.3 % *vs* 60 %, P=0.007)[21].

The mechanisms underlying the suggested association between *H. pylori* infection and chronic bronchitis remain unclear. This association might reflect either susceptibility induced by common factors or a kind of causal relationship between these two conditions. It is well known that age, sex and socioeconomic status are related with both *H. pylori* infection[1] and risk of developing chronic bronchitis[16]. However, in all mentioned studies above patients with chronic bronchitis were well matched with control subjects for these parameters. Tobacco use could be another confounding factor. Cigarette smoking is the major cause of chronic bronchitis[16]. On the other hand, data on the relation between *H. pylori* infection and smoking habits are controversial. The prevalence of *H. pylori* infection in smokers has been variously reported as low[22], normal[23], and high[24]. As the relation between smoking and *H. pylori* infection has not been clarified yet, the possible impact of cigarette smoking on both chronic bronchitis and *H. pylori* infection should be regarded as a potential limitation of the reviewed studies.

Unfortunately, there are no studies in the literature focused on the potential aetio-pathogenetic role of *H. pylori* infection in chronic bronchitis. Some authors hypothesized that the chronic activation of inflammatory mediators induced by *H. pylori* infection might lead to the development of a non-specific inflammatory process, such as chronic bronchitis[19,21]. It is well known that *H. pylori* and particularly those strains bearing the cytotoxin associated gene-A (cagA positive strains), stimulates the release of a variety of proinflammatory cytokines, including interleukin-1 (IL-1), IL-8 and tumour necrosis factor-alpha[25,26]. The eradication of *H. pylori* leads to normalization of serum cytokines levels[27]. Recent studies showed that the same cytokines might be released during the course and exacerbations of chronic bronchitis[10,11,28]. The underlying mechanisms, which induce and control this inflammatory process in chronic bronchitis, are still unclear. Therefore, we could hypothesize that *H. pylori* infection might play a proinflammatory role and co-trigger chronic bronchitis with other more specific environmental, genetic and unknown yet factors.

In conclusion, the primary evidence for an association between *H. pylori* infection and chronic bronchitis rests on serologic, case-control studies. Studies estimating the relative risk of developing chronic bronchitis for *H. pylori* infected patients and the effect of *H. pylori* eradication on the natural history of chronic bronchitis should be undertaken. The pathogenetic mechanisms underlying this association need also further evaluation. Future studies concerning this aspect should be focused on the prevalence of cagA positive Helicobacter strains and their induced proinflammatory markers, in patients with chronic bronchitis.

HELICOBACTER PYLORI INFECTION AND PULMONARY TUBERCULOSIS

Tuberculosis (TB) is a chronic bacterial infection caused by Mycobacterium tuberculosis and characterized by the formation of granulomas in infected tissues and by cell-mediated hypersensitivity. The lungs are primarily infected. However, any other organ may be involved. Although there is a lack of epidemiological evidence concerning the worldwide prevalence of TB, it has been estimated that one third of the world population is infected with Mycobacterium tuberculosis and there are ten million new cases of active TB each year. The vast majority of them occur in the developing countries, where TB remains a common health problem[29].

In 1992, Mitchell *et al* carried out a large cross-sectional study concerning the *H. pylori* epidemiology in a southern China population. They found that a history of pulmonary TB might be associated with an increased prevalence of *H. pylori* infection[30]. More recently, Woeltje *et al* assessed the prevalence of tuberculin skin test (TST) positivity in a cohort of 346 newly hospitalized patients. A history of peptic ulcer disease was one of the identified risk factors for a positive TST test (odds ratio: 4.53, P=0.017)[31]. In order to further investigate the possible association between pulmonary TB and *H. pylori* infection, Sanaka *et al* performed, in 1998, a serologic case-control study in a hospitalized population. No difference in *H. pylori* seroprevalence among 40 inpatients on antituberculosis chemotherapy for less than three months, 43 TB patients on chemotherapy for more than three months and 60 control subjects was detected (73.3 %, 65 % and 69.8 % respectively, P>0.5 in all comparisons)[32]. However, in this study the eradication of *H. pylori* by antituberculosis drugs could not be excluded. Rifampicin and Streptomycin, two drugs commonly used in antituberculosis regimens, are effective against *H. pylori* and decrease in *H. pylori* seroprevalence during antituberculosis therapy has been reported[33,34]. Therefore, we recently carried out a case-control study focused on the seroprevalence of *H. pylori* in TB patients, before the initiation of antituberculosis treatment. A total of 80 TB patients and 70 control subjects, well matched for age, sex and social

status, were recruited into this study. We found that the *H. pylori* seropositivity in the TB group was significantly higher than that of controls (87.5 % *vs* 61.4 %, P=0.02). The mean serum concentration of IgG antibodies against *H. pylori* was also significantly higher in TB patients than in control subjects (39.0±25.2 U/ml *vs* 26.1±21.2 U/ml, P=0.001)[35].

Taken together, data in the literature on the relationship between *H. pylori* infection and pulmonary TB are still insufficient. The observed frequent coexistence of both infections must be confirmed in a larger number of patients. This coexistence might reflect susceptibility to both *H. pylori* and Mycobacterium tuberculosis induced by common host genetic factors. It has been suggested that HLA-DQ serotype may contribute to enhanced mycobacterial survival and replication[36]. Recent studies showed that the same serotype is also associated with increased susceptibility to *H. pylori* infection[37,38]. Poor socioeconomic and sanitary conditions during childhood could be another factor responsible for the association between the two infections, as it is well known that in developing countries acquisition of both *H. pylori* and Mycobacterium tuberculosis occurs early in life[39,40]. Therefore, we believe that studies focused on the common, either genetic or environmental, predisposition to both bacteria are needed.

HELICOBACTER PYLORI INFECTION AND BRONCHIECTASIS

Bronchiectasis is an abnormal and permanent dilation of bronchi, due to inflammation and destruction of the structural components of the bronchial wall. Persistent or recurrent cough, purulent sputum production and/or hemoptysis are symptoms presented during the clinical course of this disorder. A wide variety of respiratory infections, toxic substances and rare congenital syndromes are associated with the development of bronchiectasis. However, a great percentage of cases are of unknown cause[41].

In 1998, Tsang *et al* found that the *H. pylori* seroprevalence in 100 patients with bronchiectasis (76 %) was higher than that in the controls (54.3 %, P=0.001). Further analysis in studied patients revealed an association between *H. pylori* seropositivity and 24-hours sputum volume (P=0.03)[42].

As far as we know, the study of Tsang *et al* is the only report in the literature concerning the association between *H. pylori* infection and bronchiectasis. The authors hypothesized that the spilling or inhalation of *H. pylori* into the respiratory tract might lead to a chronic bronchial inflammatory disorder such as bronchiectasis. However, although *H. pylori* has been identified in the tracheobronchial aspirates in mechanically ventilated patients[43], neither identification in human bronchial tissue nor isolation from bronchoalveolar lavage (BAL) fluid have been achieved yet[1]. On the other hand, recent studies have shown that inflammation in bronchiectasis is primarily cytokine-mediated[12,44]. Therefore, the activation of systemic inflammatory mediators by chronic *H. pylori* infection could represent a possible pathogenetic link between these two diseases.

In conclusion, the possible association between *H. pylori* and bronchiectasis seems intriguing and might have a pathogenetic basis. However, studies in larger series are needed to confirm this association and to clarify the underlying mechanisms. As pulmonary TB is a common cause of bronchiectasis, we believe that the increased prevalence of *H. pylori* infection in TB patients should be taken into account in the design of these future studies.

HELICOBACTER PYLORI INFECTION AND OTHER RESPIRATORY DISEASES

Lung cancer A recent study showed a higher *H. pylori* seroprevalence (89.5 %) among 50 patients with lung cancer than that in control subjects (64 %, P<0.05). The CagA strain seropositivity was about thrice as high as in controls. (63 % *vs* 21.5 % respectively, P<0.05). Lung cancer patients were characterized by a significant increase of gastrin concentration in both serum and bronchoalveolar lavage (BAL). An enhanced m-RNA expression for gastrin and its receptor, as well as for cyclooxygenase (COX)-2, in the tumor tissue was also detected. Therefore, the authors hypothesized that *H. pylori* might contribute to lung carcinogenesis, via enhancement of gastrin synthesis. Gastrin might induce increased mucosal cell proliferation of bronchial epithelium and lead to atrophy and induction of COX-2, as it happens in gastric cancer. Finally, the authors proposed that *H. pylori* should be eradicated in lung cancer patients, in order to reduce the *H. pylori* provoked hypergastrinemia and COX-2 expression[45].

Chronic bronchitis, which is associated with both lung cancer and *H. pylori* infection, might be a confounding factor in this study. Moreover, although some authors have also showed an increased gastrin concentration in serum and BAL fluid in lung cancer patients[46,47], others did not confirm this finding[48]. Therefore, we believe that before adapting the *H. pylori* eradication in lung cancer patients, further studies are needed to examine whether the reported epidemiological association between these two diseases has a pathogenetic basis.

Bronchial asthma In 2000, Tsang *et al* estimated the prevalence of *H. pylori* infection in a cohort of 90 patients with bronchial asthma. *Helicobacter pylori* seroprevalence did not differ significantly between asthmatic and control subjects (47.3 % *vs* 38.1 %, P>0.05), while serum concentration of IgG antibodies against *H. pylori* did not correlate with spirometric values and duration of asthma. The authors concluded that bronchial asthma might not be associated with *H. pylori* infection[49]. Moreover, as far as we know there is a lack of a theoretical hypothesis that might explain a possible association between these two diseases. Therefore, we believe that our knowledge on the association between *H. pylori* infection and respiratory diseases is unlikely to be advanced by more studies concerning the prevalence of *H. pylori* infection in patients with bronchial asthma.

CONCLUSIONS-FUTURE CHALLENGES

At present, the primary evidence for a link between *H. pylori* infection and respiratory diseases rests on case-control studies, concerning relatively small numbers of patients. Future studies should be large enough for moderate-sized effects to be assessed or registered reliably. The activation of inflammatory mediators by *H. pylori* infection might be the pathogenetic mechanism underlying the observed associations. Therefore, the role of genetic predisposition of the infected host, the presence of strain-specific virulence factors and the serum concentration of proinflammatory markers in *H. pylori* infected patients with respiratory diseases needs further evaluation. Finally, randomized control studies should be undertaken, in order to clarify the effect of the *H. pylori* eradication on the prevention, development and natural history of these disorders.

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