

Helicobacter pylori and Respiratory Diseases

Subjects: [Gastroenterology & Hepatology](#) | [Respiratory System](#)

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Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium involved in the development of gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue. Unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B12 deficiency have also been related to *H. pylori* infection, whereas for other extra-gastric diseases, the debate is still open. In this entry, we evaluate and discuss the potential involvement of *H. pylori* infection in the pathogenesis of several respiratory diseases.

respiratory diseases

asthma

chronic obstructive pulmonary disease

1. Introduction

Helicobacter pylori (*H. pylori*) infection is globally widespread, usually acquired during childhood, and often related to low socio-economic class ^[1]. Although the precise mode of transmission remains unproven, it has been shown that such a microorganism spreads directly from one person to another, mainly by fecal-oral or oral-oral routes ^[2]. This microaerophilic, Gram-negative bacterium is usually located within the mucus layer of the stomach, and certain ultrastructural details found on its surface (sheathed flagella and urease) are involved in its ability to survive in the surrounding hostile environment ^[3]. Thus, this disproves the ancient conception of the impossibility for microorganisms to survive in the gastric compartment due to acidity ^[4]. It is well known that *H. pylori* infection may lead to gastritis, peptic ulcer disease (PUD), gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma ^[5], although most infected subjects remain asymptomatic. Furthermore, in the past few years, the possible role of *H. pylori* in many extra-gastric diseases has been investigated ^{[6][7][8]}. Among these, accumulating evidence also supports an association with neurodegeneration ^[9] and nonalcoholic fatty liver disease ^[6], although some controversy still exists. However, only unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency have been associated with the latter infection, as reported in the fifth edition of the Maastricht/Florence Consensus Report (2017) ^[10].

Respiratory diseases represent a leading cause of morbidity and mortality in the world. For this reason, as stated by the World Health Organization (WHO), the prevention, control and cure of these diseases must be a top priority in global decision-making in the health sector ^[11]. Currently, infections are the leading cause of respiratory diseases in both children and adults, with variable outcomes depending on the causal agent as well as on the host and environmental factors. Since known etiologic agents and risk factors explain the pathogenesis of only a proportion of cases, investigating whether non-traditional agents have a causal role in the pathogenetic steps of respiratory diseases is of primary importance.

Early epidemiologic studies on the relationship between *H. pylori* infection and respiratory diseases have been supported by the findings on animal models showing that the presence of the microorganisms in the gastric compartment could be associated with lung injury, as indicated by the increased expression of inflammatory mediators and markers of endothelial dysfunction [12]. Over time, a series of publications, mainly reporting the findings of epidemiologic studies, has focused on this issue and has provided controversial results.

2. Analysis on Results

Considering that several studies did not show a causal relationship, but often, an inverse association between *H. pylori* infection and allergic asthma [13][14], a protective effect of this microorganism against allergic diseases including asthma, especially in children and young people, was hypothesized around fifteen years ago (the so-called “hygiene hypothesis”). The authors associated the reduction of *H. pylori* prevalence with the rise in asthma cases as well as other allergic disorders in children, assuming a possible relationship [15]. Over time, multiple epidemiological studies were performed on this topic and a recent meta-analysis, including 18 observational studies with 17,196 enrolled children, reported a significant negative association between *H. pylori* and the risk for childhood asthma (odds ratio [OR] = 0.68; 95% confidence interval [CI]: 0.54–0.87; $p = 0.002$), particularly in those harboring the more virulent strains (according to cytotoxin-associated gene A [CagA] status) (OR = 0.58; 95% CI: 0.35–0.96; $p = 0.034$). No significant difference among studies regarding participant age, geographical region, study design and diagnostic method for *H. pylori* detection was observed [16]. In recent years, the association between asthma or other allergic diseases and *H. pylori* has been intensively investigated. In a case-control study including more than 10,000 patients, *H. pylori* infection was found in 31%, asthma in 10.4%, and allergic rhinitis in 16% of them, without any significant association; however, in patients with abdominal obesity, *H. pylori* infection was associated with 30-40% reduced OR of asthma and 25% reduced OR of allergic disorders [17]. Moreover, in a case-control study performed in Greece including 27 pediatric patients with asthma and 54 controls, an inverse association between *H. pylori* and asthma was confirmed (OR = 0.1; 95% CI: 0.039–0.305; $p = 0.026$) [18]. In a cohort study, 16% of children who were uninfected at 2 and 10 years of age developed asthma at 16 years vs. none of the children with *H. pylori* infection at 2 years of age [19] (**Table 1**).

Table 1. Summary of the cumulative results of the main studies included.

Respiratory Disease		Result	Reference	Publication Year
	Meta-analysis of 18 studies	Negative association with <i>H. pylori</i> infection	[15]	2021
ASTHMA	Case-control study including 10,000 patients	Only in obese patients <i>H. pylori</i> associated with 30–40% OR of asthma ↓	[16]	2019
	Cohort study	16% of children uninfected at 2 and 10 years developed asthma	[18]	2020

Respiratory Disease		Result	Reference	Publication Year
		at 16 years versus none of the children with <i>H. pylori</i> at 2 years		
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	Case-control study including patients with type 2 diabetes mellitus and controls	In diabetics, seropositivity was significantly associated with chronic bronchitis	[20]	2020
	Retrospective cohort study (Taiwan)	Significant association between <i>H. pylori</i> and COPD	[21]	2017
	Case-control study (Korea, country with high burden of <i>H. pylori</i>)	No association between <i>H. pylori</i> and COPD	[22]	2016

Nevertheless, some authors consider *H. pylori* only a marker of poor household hygiene. This stems from the evidence from studies testing the hypothesis of a protective effect in relation to asthma in populations with poor hygiene and low *H. pylori* prevalence (for example in Malaysia and Indonesia), which did not confirm this effect [23]. Furthermore, the results of studies and consequently meta-analyses could be affected by the diagnostic method used to diagnose *H. pylori* infection (mainly serology that does not discriminate between current and past infection).

In this context, it has been hypothesized that the inhalation of *H. pylori* or its endotoxins into the respiratory tract could lead to a chronic activation of inflammatory mediators. In 1998, Tsang et al. first described a significantly higher serum IgG positivity against *H. pylori* in 100 consecutive patients with bronchiectasis compared to healthy controls (76.0% vs. 54.3% respectively, $p = 0.001$) [24]. The following year, Tsang et al. reported a higher *H. pylori* CagA+ seroprevalence in bronchiectasis patients than in controls (24% vs. 11.7%, $p = 0.03$) [25]. However, Angrill et al. were unable to detect *H. pylori* by histochemical and immunochemical staining in bronchial tissue from patients with bronchiectasis and positive serology [26]. Similarly, Gülhan et al. did not find evidence of *H. pylori* DNA in either BAL fluid or in lung tissues by using PCR, from patients with bronchiectasis. In addition, they did not find a statistically significant difference in anti- *H. pylori* IgG level between patients and controls [27]. Furthermore, in another study, there were no significant differences between bronchiectasis patients and controls regarding *H. pylori* positivity in BAL fluid, gastric juice, and urea breath test [28].

Few studies have examined a possible correlation between *H. pylori* and cystic fibrosis. Drzymala-Czyż et al. assessed the prevalence of *H. pylori* infection, using breath tests with isotope-labeled urea in 79 cystic fibrosis patients compared to 302 healthy controls, but no significant difference was found [29]. In a study by Yahav et al., the authors found a lower prevalence of *H. pylori* infection in cystic fibrosis patients than in non-cystic fibrosis controls (16.6% and 30.0%, respectively), assessed by using specific monoclonal antibodies for fecal *H. pylori* antigen. However, due to the small number of cystic fibrosis patients enrolled ($n = 30$) in this study, the difference was not statistically significant [30]. A seroprevalence study, conducted by Israel et al., included 70 cystic fibrosis patients. The authors reported an initial seropositivity rate of 47% (33/70) for *H. pylori* IgG antibody, but after pre-

adsorption of these sera with *Pseudomonas* proteins, a marked decrease in *H. pylori* seropositivity (8%, 6/70) was observed, highlighting a cross-reactivity between *H. pylori* antigens and *Pseudomonas* antibodies [31].

3. Conclusions

The question as to whether *H. pylori* is an innocent bystander, a protective agent or a trigger of respiratory diseases cannot yet be answered. On the other hand, these are often multifaceted disorders, the mechanism of which cannot be explained by only one cause. Hence, the need for larger studies with appropriate epidemiological design to investigate a potential causal relationship between *H. pylori* infection and respiratory diseases is evident.

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