Helicobacter pylori Infection and the Respiratory System: A Systematic Review of the Literature

Maximilian V. Malfertheiner^a Arne Kandulski^b Jens Schreiber^a
Peter Malfertheiner^b

Departments of ^aPneumology and ^bGastroenterology, Hepatology and Infectious Diseases, Otto von Guericke University Magdeburg, Magdeburg, Germany

Key Words

Asthma • *Helicobacter pylori* • Inflammation • Lung •
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Abstract

Background: Recent studies suggest an increased *Helicobacter pylori* prevalence in patients with various extradigestive inflammatory diseases. Similar to *H. pylori* infection, many respiratory diseases are characterized by chronic inflammation as well as increased immune response. Recent studies have evaluated the relation between various respiratory disorders and *H. pylori* infection. The aim of this systematic review was to scrutinize the relevant literature and the mechanisms that could underlie a role for *H. pylori* infection in respiratory diseases. **Methods:** Relevant literature regarding pathophysiological mechanisms and clinical epidemiology of *H. pylori* and different respiratory diseases has been systematically identified and analyzed by two independent reviewers according to a PubMed search for English language (until week 14, April 2010). **Conclusions:** At present, there is no definite proof of a causal relationship between *H. pylori* and respiratory diseases. Both *H. pylori* and various respiratory diseases are characterized by the release of proinflammatory cytokines and attraction of granulocytes as well as B- and T-cell-mediated response, though a pathophysiological association has not been proven. Neither the role of

genetic predisposition of the host nor the presence of virulence factors nor the impact of *H. pylori* eradication have been studied in detail and definitely need further evaluation.

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Introduction

Helicobacter pylori colonizes the gastric mucosa of approximately 50% of the world population [1]. Since Marshall and Warren [2] first described *H. pylori* in the pathogenesis of gastric and duodenal ulcer disease in 1982, it has been a subject of extensive research. *H. pylori* is the main cause of chronic gastritis [2], peptic ulcer disease [3], low-grade lymphoma of gastric mucosa-associated lymphoid tissue [4, 5] and the most important risk factor for gastric adenocarcinoma.

An increased *H. pylori* prevalence has been reported in patients with various extradigestive inflammatory diseases including autoimmune, vascular and skin diseases [6–9]. The proof of a causal relationship between *H. pylori* and these extradigestive diseases is missing in most of these conditions. *H. pylori* has been associated with many respiratory disorders, including chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, lung cancer and tuberculosis. Common features of *H. py-*

lori infection and chronic lung diseases are chronic inflammation as well as increased immune response. The aim of this review was to scrutinize the relevant literature and the underlying mechanisms of the potential relation of *H. pylori* infection and respiratory diseases.

Methods

Literature Research

Relevant literature regarding pathophysiological mechanisms and clinical epidemiology of *H. pylori* and different diseases of the respiratory tract has been systematically identified according to a PubMed search for English language. By combination of *H. pylori* with the terms *lung*, *respiratory tract*, *COPD*, *lung cancer*, *asthma*, *bronchiectasis*, *tuberculosis*, *cystic fibrosis*, *pneumonia* and *sarcoidosis*, two independent researchers [specialists in pneumology (M.V.M.) and gastroenterology (A.K.)] generated a list of original research articles published in English, peer-reviewed journals until week 14, April 2010 (table 1).

Potentially relevant articles were retrieved and the reference lists were reviewed to identify studies that may have been missed.

Inclusion and Exclusion Criteria

In this review, we either included clinical studies that met epidemiological criteria or pathophysiological studies of both *H. pylori* and a specific respiratory disease ('key word'). Studies were excluded if *H. pylori* and respiratory diseases had not been their primary aim.

Background

H. pylori Infection and Immunological Determinants in Human Physiology

H. pylori infection is usually acquired in early childhood. It leads to chronic inflammation of the gastric mucosa, often with a predominant pattern of gastritis either in the antrum or corpus and with abnormal release of gastrin, somatostatin and other neuropeptides. The individual phenotypic expression of *H. pylori*-induced gastritis is dependent on bacterial virulence factors, host immune response and environmental factors. In antrum-predominant gastritis, acid secretion is increased, whereas corpus-predominant gastritis is characterized by the development of intestinal metaplasia and glandular atrophy as well as impaired gastric acid secretion [10]. The infection triggers a marked local and systemic immune response that results in a lifelong persistence and only rarely in the elimination of the bacteria [11].

The host immune response is characterized by the gastric mucosal infiltration by polymorphonuclear cells and lymphocytes that orchestrate the release of various cyto-

Table 1. Systematic research of the literature regarding *H. pylori* (PubMed database up to week 14, April 2010)

Key words	Initial literature research	Accepted relevant articles for analysis
Lung cancer	76	4
COPD	21	7
Bronchiectasis	14	6
Asthma	80	21
Tuberculosis	134	11
Cystic fibrosis	13	5
Sarcoidosis	14	3
Pneumonia	51	0

kines and attract and activate other immune cells. The *H. pylori* antigen presentation and recognition by gastric epithelial cells, dendritic cells and macrophages induces a complex cytokine milieu promoting the differentiation of various T cell lineages (Th1, Th2 and Treg/Th17). Numerous studies reported a rather Th1-dominated immune response (TNF- α , IL-1 β , IFN- γ) in *H. pylori*-induced gastritis (fig. 1) [12–21]. Recent studies reported about different immunological determinants concerning the subpopulations of regulatory T cells in *H. pylori*-infected patients [17–22].

H. pylori is characterized by a high level of genetic diversity and a variety of specific virulence factors (i.e. *cag* pathogenicity island) with key functions in challenging the host immune response and therefore also having a systemic effect [10, 23–25].

Mechanisms by Which *H. pylori* Colonization Might Affect the Lung

Mechanisms that are discussed regarding the relationship of *H. pylori* infection and lung diseases are: (a) systemic effect of gastrointestinal peptides (gastrin, somatostatin), cytokine release from the gastric mucosa and systemic effects of the adaptive immune system, and (b) direct damage and chronic airway inflammation by aspiration or inhalation. *H. pylori* has been isolated from tracheal secretion of intubated patients; however, it has never been detected in human bronchial tissue or isolated from bronchoalveolar lavage fluid [26].

The release of proinflammatory cytokines, including IL-1 β , IL-8 and TNF- α [27], is involved in the immunopathogenesis of chronic pulmonary diseases. *H. pylori* eradication and normalization of serum cytokine levels offers a model to study these effects on extradigestive and pulmonary diseases [28] (fig. 2). Gastrin release during

Fig. 1. Immunological determinants of *H. pylori* infection. Antigen presentation and recognition by dendritic cells (DCs) in the mucosa-associated tissue. Local and systemic Th1-dominated immune response by the secretion of IL-8, IL-1 β , and TNF- α . Possible interaction with regulatory T cell subpopulation by secretion of cytokines and cell-cell contact-dependent mechanisms.

Fig. 2. Interaction of *H. pylori* with different pulmonary diseases. Interaction of *H. pylori* with different pulmonary diseases by different pathophysiological and immunological mechanisms.

H. pylori infection is always increased, and highest in chronic gastritis with advanced mucosal changes (i.e. atrophy) [29]. As lung tissue is also derived from embryonic endodermal cells, neurohormonal regulation and malignant transformation might underlie similar pathways [30].

Lung Cancer and *H. pylori*

Lung cancer is by far the leading cause of cancer-related death worldwide [31]. The environmental causes of lung cancer have been the focus of intense research for more than 50 years. Tobacco smoking accounts for >80%

of the attributable risk for lung cancer. Known environmental causes are a variety of occupational agents and indoor and outdoor air pollution [32, 33].

Concerning *H. pylori*, Gocyk et al. [34] described an increased *H. pylori* seroprevalence in a cohort of 50 patients with lung cancer compared to controls (89.5 vs. 64%). Analyzing CagA-positive strains, they even found more significant differences compared to controls (63 vs. 21.5%, respectively). Since then, inconsistent results have been reported. Studies by Najafizadeh et al. [35] or Philipou et al. [36] did not confirm the previous results of higher seroprevalence of *H. pylori* in lung cancer patients. Analyzing VacA and CagA, a study focused on non-small cell carcinoma reported that both VacA and CagA sero-

Table 2. Epidemiological studies about *H. pylori* and lung cancer

Author	Publication year	Patients/controls	<i>H. pylori</i> prevalence	CagA/VacA status	Type of lung cancer
Gocyk et al. [34]	2000	50/100	89.5/64 ($p < 0.05$)	–	N/A
Philippou et al. [36]	2004	72/68	61.1/55.9 ($p = 0.23$)	–	all
Najafizadeh et al. [35]	2007	40/40	52.5/45.0 ($p = 0.65$)	–	all
Ece et al. [37]	2005	43/28	93/42 ($p < 0.05$)	+	NSCLC

positivity were high in lung cancer patients, but only VacA positivity was statistically significant when compared with control subjects [37] (table 2).

One study also investigated gastrin in lung cancer patients and described high gastrin concentration in both serum and bronchoalveolar lavage [34]. Other studies presented inconsistent results [38–40].

Postulated pathophysiological mechanisms of gastrin in lung cancerogenesis include increased mucosal cell proliferation of bronchial epithelium, COX-2-mediated effects and the induction of bronchoepithelial atrophy [34]. As there exist no confirmatory data, the contribution of *H. pylori* to lung carcinogenesis remains hypothetical. For the future, results in a larger series of patients are needed to confirm this hypothetical association and profound basic and translational research needs to focus on the pathophysiological mechanisms.

COPD and *H. pylori*

COPD is an umbrella term for chronic bronchitis, emphysema and various other pulmonary disorders. Most often, COPD is due to tobacco smoking, but can also originate from other airborne irritants such as coal dust, asbestos or solvents, as well as congenital conditions such as α_1 -antitrypsin deficiency.

An association of COPD with peptic ulcer disease was reported already back in 1968. Since then, epidemiological studies reported the prevalence of COPD in peptic ulcer patients to be increased two- to threefold compared with ulcer-free controls [41–43]. Furthermore, chronic bronchitis and emphysema were recognized as a major cause of death among patients with peptic ulcer disease [44]. Cigarette smoking was long thought to be the major factor responsible for the development of both disorders. However, it is now clear that the role of tobacco consumption is only a facultative factor in the *H. pylori* infection-driven peptic ulcer disease [10].

A prospective study in 60 patients with chronic bronchitis reported an increased *H. pylori* seroprevalence (81.6 vs. 57.9%) compared to controls [45]. Several other studies confirmed this result. Rosenstock et al. [46] showed a higher COPD prevalence in *H. pylori* IgG-seropositive women compared with uninfected women. Jun et al. [47] found an *H. pylori* seroprevalence of 86.9% in patients with chronic bronchitis compared to 60.4% in controls, also with significant CagA seropositivity. Two case-control studies from Greece demonstrated anti-*H. pylori* and anti-CagA seropositivity being significantly higher in patients with COPD than in control subjects [48, 49]. A more recent Turkish study [50] concerning *H. pylori* seroprevalence in a subgroup of COPD patients (those with chronic bronchitis) described similar results. They found that *H. pylori* seropositivity in bronchitic patients was significantly higher than that in controls (66.1 vs. 57.7%, respectively). Investigating spirometric values and disease activity, no significant differences were found between *H. pylori*-infected and noninfected patients with COPD [48], although there was one study by Gencer et al. [51] that showed a slight correlation of *H. pylori* IgG levels with the severity of COPD.

A causal role for *H. pylori* in COPD has not been established. Both *H. pylori* infection and the pathogenesis of COPD are related to older age, male sex and low socioeconomic status, and COPD patients were well matched for all parameters. However, as *H. pylori* infection is usually acquired during childhood, matching for socioeconomic status should be performed for childhood and not for the time of study. Therefore, inappropriate matching for socioeconomic status should be regarded as a limitation of all mentioned studies. Cigarette smoking could be another confounding factor. It is well known that tobacco use represents the major cause of COPD. On the other hand, data on the relation between *H. pylori* infection and smoking habits are controversial. The relation between tobacco use and *H. pylori* remains uncertain, and the possible impact of cigarette smoking on both COPD de-

velopment and *H. pylori* infection should be regarded as a limitation of all reviewed studies. There are no studies in the literature that focused on the potential ethiopathogenetic role of *H. pylori* infection in COPD.

As reported above, *H. pylori* stimulates the release of proinflammatory cytokines. Chronic inflammation is a prominent feature of COPD, as shown by the presence in the airway of activated neutrophils and macrophages and the increased number of inflammatory mediators [52–54]. Recent studies showed that cytokines identical to those stimulated by *H. pylori* are released during the course and exacerbations of COPD, and especially IL-8 might also be implicated in the pathogenesis of the disease, but there are no data about the influence of *H. pylori* on the inflammatory changes of the bronchoepithelium so far [55–57]. *H. pylori* infection might play a pro-inflammatory role and co-trigger COPD with other more specific environmental, genetic and yet unknown factors. The association between *H. pylori* infection and COPD is based only on serologic case-control studies with low socioeconomic status and tobacco abuse as confounding factors.

Bronchiectasis and *H. pylori*

Bronchiectasis is characterized by abnormal and permanent dilation of bronchi due to chronic inflammation and destruction of the structural components of the bronchial wall. High levels of proinflammatory cytokines are present in airway secretions, and infiltrating immune cells in the airway lumen are dominated by neutrophils. In active bronchiectasis, bronchial damage is thought to be mediated by neutrophil-derived mediators as proteases and cytokines that are released in response to bacterial infection [58, 59].

The first report on higher *H. pylori* seroprevalence in patients with bronchiectasis was made by Tsang et al. in 1998 [60]. They also found a positive correlation between *H. pylori* seropositivity and 24-hour expectorated sputum volume. A second study demonstrated a much higher *H. pylori* CagA status in patients with bronchiectasis than in controls ($p = 0.03$) [61].

As bronchiectasis and gastroduodenal ulcers are both characterized by inflammatory damage, there are of course similarities in the pathogenesis of both diseases. In both conditions, there is exposure to luminal bacteria that leads to extensive recruitment of neutrophils and T lymphocytes into the submucosa and cytokine release of IL-8, TNF- α and IL-1 β [62, 63]. Despite the similarities

in the pathogenesis of bronchiectasis and peptic ulcer disease, and the high seroprevalence of *H. pylori* in bronchiectasis, a possible pathogenetic role of *H. pylori* in bronchiectasis remains unexplored.

One suggested hypothesis is that the inhalation of the bacterium into the respiratory tract might lead to a chronic bronchial inflammatory disorder such as bronchiectasis. However, neither the identification of *H. pylori* in human bronchial tissue nor the isolation from bronchoalveolar lavage fluid have yet been achieved [61, 64]. Moreover, investigations have been unsuccessful to identify *H. pylori* in culture or histopathological examinations of protected catheter brush and biopsy specimens from bronchiectasis [65].

In chronic bronchiectasis, the chronic airway inflammation is predominantly cytokine mediated [62]. Therefore, the activation of systemic inflammatory mediators by chronic *H. pylori* infection could explain the increased prevalence of *H. pylori* infection in patients with chronic active bronchiectasis [60].

Tuberculosis and *H. pylori*

One third of the world's population has been estimated to be infected with *Mycobacterium tuberculosis* and there is an incidence of 10 million new cases of active tuberculosis per year. The vast majority of them occur in developing countries, where tuberculosis remains a common health problem.

It is well known that patients with peptic ulcers are more prone to tuberculosis than individuals who are ulcer-free [66]. Previous studies have indicated that patients with tuberculosis may have a higher *H. pylori* prevalence than healthy controls [67]. Filippou et al. [68] conducted a study in Greece and observed a 87.5% seroprevalence of *H. pylori* in 80 consecutive patients compared to a significantly lower 61.4% in 70 controls ($p < 0.004$). Another study in a Chinese population indicated that a history of pulmonary tuberculosis might be associated with an increased prevalence of *H. pylori* infection [69]. However, Sanaka et al. [70] performed a serology-based case-control study in a hospitalized population and found no significant difference in *H. pylori* seroprevalence between a group of 40 inpatients who had been on antituberculosis therapy for more than 3 months and a group of 60 control inpatients. In addition, Tsang et al. [60] showed no differences in seroprevalence of *H. pylori* between healthy volunteers and patients with tuberculosis.

Table 3. Epidemiological (cross-sectional and case-control) studies about *H. pylori* and asthma

Author	Publication year	Patients/controls	<i>H. pylori</i> measurement	OR (95% CI) in relation to <i>H. pylori</i> +
McCune et al. [81]	2003	3,244	¹³ C-urea breath test	0.78 (0.59–1.05)
Shiotani et al. [75]	2007	777	IgG ELISA	0.65 (0.45–1.06)
Janson et al. [78]	2007	1,249	IgG ELISA	0.55 (0.34–0.89)
Chen and Blaser [77]	2008	7,663	IgG ELISA	0.79 (0.63–0.99) ^a
Chen and Blaser [79]	2007	7,412	IgG ELISA	0.41 (0.24–0.69)
Fullerton et al. [74]	2008	2,437	IgG ELISA	1.09 (0.77–1.54)
Tsang et al. [82]	2000	90/97	IgG ELISA	1.55 (0.83–2.90)
Bodner et al. [83]	2000	97/208	IgG ELISA	0.50 (0.20–1.50)
Jun et al. [80]	2005	46/48	IgG ELISA	1.10 (0.45–2.69) 1.20 (0.39–3.69) ^a
Reibman et al. [76]	2008	318/208	IgG ELISA	0.94 (0.57–1.57) 0.63 (0.41–0.98) ^a

^a cagA+.

The HLA-DQ serotype may contribute to enhanced mycobacterial survival and replication [70]. The same serotype is also associated with increased susceptibility to *H. pylori* infection [71, 72]. Currently, our knowledge about a possible association between *H. pylori* infection and tuberculosis is entirely based on the above-mentioned serologic case-control studies, while some other studies denied this assumption. Further, the pathogenetic mechanisms involved remain completely unclear.

Bronchial Asthma and *H. pylori*

In recent years, there has been a rise in the prevalence of bronchial asthma in developed countries. An environmental factor for this observation has been assumed and some of the leading candidates besides tobacco smoke, air pollution and allergen exposure also include exogenous infections and microbial substances in the environment. In addition to these exogenous causes, a change of the indigenous microbiota can be hypothesized as underlying pathomechanism. Therefore, the decrease in *H. pylori* infection in developed countries is associated with an

increasing incidence of bronchial asthma by the advocates of the ‘hygiene hypothesis’ [73]. There are a number of cross-sectional and case-control studies addressing this association with controversial results (table 3) [74–83]. Worth mentioning are the studies which considered CagA status. These studies have consistent results regarding an inverse relation of *H. pylori* infection and bronchial asthma [76, 77, 80].

There exists a pathogenetic mechanism hypothetically explaining an inverse relation. Bronchial asthma is orchestrated by T cells producing Th2 cytokines, such as IL-4 and IL-5, and inhibited by Th1 responses. *H. pylori* preferentially elicits a Th1 mucosal immune response with the production of IFN- γ and IL-12. Among several bacterial factors, the neutrophil-activating protein of *H. pylori* (HP-NAP) not only plays a key role in driving Th1 inflammation but it is also able to inhibit Th2 responses in vitro and in vivo in allergic bronchial asthma, in humans and mice [13]. Both systemic and mucosal administrations of HP-NAP are successful in reducing eosinophilia, IgE and systemic Th2 cytokines at the bronchial level [13].

Cystic Fibrosis and *H. pylori*

Cystic fibrosis (CF) is a multisystem disease that is associated with pancreatic insufficiency, malabsorption, liver disease, chronic sinusitis, CF-related diabetes, male sterility, and osteoporosis, among others. But it is the chronic pulmonary inflammation and infection that cause most of the CF morbidity and mortality.

Only a small number of publications can be found addressing *H. pylori* and CF [84–87]. A study by Israel et al. [85] is the only study addressing the prevalence of *H. pylori* infection in CF patients; it shows a lower prevalence than in similarly aged non-CF controls [87].

A known problem testing CF patients for *H. pylori* is a cross-reactivity between solid-phase *H. pylori* antigens and anti-Pseudomonas antibodies. So a high index of suspicion should be assumed in evaluating results of serologic *H. pylori* tests in this population. To receive more confidential results, a preadsorption of CF sera with Pseudomonas proteins should be used in serologic testing [85, 88].

A disguise to a definite prevalence of *H. pylori* in CF patients may also be a considerably higher usage of antibiotics with resulting *H. pylori* eradication in CF patients compared to controls.

Sarcoidosis and *H. pylori*

Sarcoidosis is a systemic disease with a 90% predilection for the lungs; however, any organ can be involved. Gastrointestinal involvement is rare, but within the gastrointestinal system, gastric involvement is the most common. The exact cause of sarcoidosis is unknown. The current working hypothesis is that in genetically susceptible individuals sarcoidosis is caused through alteration in immune response after exposure to an environmental, occupational, or infectious agent [89].

Gastric involvement in systemic sarcoidosis has been associated with *H. pylori* infection several times in the past [90, 91], but a causal association is unlikely. Hernon et al. [92] performed a study measuring *H. pylori* antibody titers in sarcoidosis patients and healthy volunteers. As a result, they found significantly higher IgG titers against *H. pylori* and urease in the sarcoidosis patients. If the immunologic reaction to *H. pylori* contributes to sarcoid granuloma formation, it warrants further investigation.

Idiopathic granulomatous gastritis is a granulomatous disease with histological findings similar to sarcoidosis, but sole involvement of the stomach. It is a rare disorder of the stomach and a rule-out diagnosis. It has been as-

sociated with *H. pylori* infection in a number of case reports [93, 94] unless a causative pathogenic relation is missing.

Conclusion

At present, there is no definite proof of a causal relationship between *H. pylori* and respiratory diseases. All available data are based on epidemiological cross-sectional studies, though case-control studies could never prove a causal relationship. Important confounders in *H. pylori*-associated lung diseases are poorer socioeconomic status and tobacco use. The release of proinflammatory cytokines and attraction of granulocytes as well as B- and T-cell-mediated responses are detected in both *H. pylori* and various respiratory diseases, but investigations failed to prove a pathophysiological association so far. Furthermore, the cancerogenesis by the presence of gastrin does not prove a causal relationship between *H. pylori* infection and lung cancer. Neither the role of genetic predisposition of the host nor the presence of strain-specific virulence factors (CagA and VacA) nor the impact of *H. pylori* eradication have been studied in detail and definitely need further evaluation.

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