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TOPIC HIGHLIGHT

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An association between *Helicobacter pylori* and upper respiratory tract disease: Fact or fiction?

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Abstract

Helicobacter pylori (*H. pylori*) is a major cause of chronic gastritis and gastric ulcers and considerable evidence supports the notion that infection with this bacterium is also associated with gastric malignancy in addition to various other conditions including pulmonary, vascular and autoimmune disorders. Gastric juice infected with *H. pylori* might play an important role in upper respiratory tract infection. Although direct and/or indirect mechanisms might be involved in the association between *H. pylori* and upper respiratory tract diseases, the etiological role of *H. pylori* in upper respiratory tract disorders has not yet been fully elucidated. Although various studies over the past two decades have suggested a relationship between *H. pylori* and upper respiratory tract diseases, the findings are inconsistent. The present overview describes the outcomes of recent investigations into the impact of *H. pylori* on upper respiratory tract and adjacent lesions.

Key words: Paranasal sinus; Ear; Adenoid; Oral cavity; Pharynx; Larynx; Upper respiratory tract; Cancer

Core tip: This review evaluates the role of *Helicobacter pylori* (*H. pylori*) in the upper respiratory system. Many studies have reported the presence of *H. pylori* in the upper respiratory tract, but their findings have varied. A definitive relationship between *H. pylori* and upper respiratory tract disorders has not been established, and further controlled studies are required.

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INTRODUCTION

The Gram-negative bacterium *Helicobacter pylori* (*H. pylori*) resides in the human stomach, which was formerly considered a sterile environment due to its low pH[1]. Permanent *H. pylori* infection is often acquired early in life[2]. Numerous studies have shown that *H. pylori* is the major cause of stomach inflammation, and it is recognized as a key factor in the development of upper gastrointestinal tract pathologies including peptic ulcer disease, gastric cancer, extragastric intestinal malignancies and gastric mucosal-associated lymphoid tissue lymphoma[3-10].

Among the known *H. pylori* virulence factors that include cytotoxin-associated gene A product (CagA), vacuolating cytotoxin (VacA), outer inflammatory pro-

Table 1 Detection of *Helicobacter pylori* in investigations of relationships between *Helicobacter pylori* and rhinitis/sinusitis

Ref.	Patients (*n*)	Samples	Methods	Positive results
Rhinitis				
Cellini *et al*[43]	42	Nasal mucus	Culture	0%
Imamura *et al*[44]	211	Blood	ELISA	44.8%
Sinusitis				
Ozyurt *et al*[52]	32	Nasal polyp	PCR	59.4%
Szczygielski *et al*[53]	61	Nasal polyp	Urease test	0%
Kaviani *et al*[54]	37	Nasal polyp	Urease test	24.3%
		Blood	ELISA (IgG)	66.2%
Cvorovic *et al*[55]	23	Nasal polyp	Urease test/giemsa staining	26.1%
Včeva *et al*[57]	35	Nasal polyp	PCR	28.6%
		Blood	ELISA	85.7%
Burduk *et al*[58]	30	Nasal polyp	PCR	100%
Morinaka *et al*[59]	11	Nasal and maxillary sinus tissues	PCR	18.2%
			Urease test	27.3%
			Culture	0%
			IHC	63.6%
Ozdek *et al*[60]	12	Ethmoid mucosa	PCR	33.3%
Koc *et al*[61]	30	Nasal polyp	IHC	20%
		Blood	ELISA	86.7%
Kim *et al*[62]	48	Intranasal tissue	Urease test/IHC	25%
Jelavic *et al*[63]	40	Nasal polyp	IHC	70%
Ozcan *et al*[64]	25	Nasal polyp	Urease test	4%
			IHC	0%
		Blood	ELISA	24%
Dinis *et al*[71]	15	Sinonasal tissue	PCR	19%
Nemati *et al*[72]	25	Nasal polyp	PCR	0%
			Culture	0%
			Urease test	0%

IHC: Immunohistochemistry; ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction.

tein and duodenal ulcer promoting[11], VacA and CagA have been the most thoroughly investigated in an effort to understand the pathogenicity of this bacterium. VacA is a pore-forming toxin that disrupts cell polarity in the gastric mucosa, promotes the apoptosis of epithelial cells, and inhibits T cell proliferation. CagA is an immunodominant antigen that is translocated into gastric epithelial cells through the Cag type Ⅳ secretion system encoded by *cag* pathogenicity islands[12]. *H. pylori* strains that express CagA are associated with an increased risk of gastric cancer. In addition to these local interactions, *H. pylori* impairs T cell-mediated immunity *via* systemic mechanisms[13].

Systemic immune and inflammatory responses to *H. pylori* might be related to extra-gastrointestinal system diseases[13]. Recent studies have identified a potential relationship between *H. pylori* infection and the pathogenesis of cardiovascular, neurological, dermatological, immunological, hematological, hepatobiliary, ophthalmological and gynecological diseases, as well as diabetes mellitus[14-23]. A role of *H. pylori* in the development of lower respiratory disease has also been suggested, but a pathophysiological association has not been proven[24-28].

The impact of gastric *H. pylori* infection on the pathogenesis of gastroesophageal reflux disease (GERD) is controversial[29,30], but *H. pylori* can survive for a certain period in gastric juice in the esophagus[31]. Gastric juices infected with *H. pylori* and systemic immune responses to gastric *H. pylori* infection might play a causative role in upper respiratory diseases[32-34]. In contrast, the findings of recent cross-sectional studies indicate that the risk of developing childhood- or early-onset allergic asthma, allergic rhinitis and atopic dermatitis is decreased in carriers of *H. pylori* compared with non-infected individuals[35-40], indicating that *H. pylori* can have both harmful and beneficial effects in patients with upper respiratory diseases.

Although the pathogenicity of *H. pylori* in gastrointestinal lesions has been extensively studied, the role of this bacterium in upper respiratory tract disorders is under debate. The present review summarizes current findings regarding the relationship between *H. pylori* and upper respiratory tract diseases.

RHINITIS

Allergic rhinitis is the most widespread type of chronic rhinitis, and it is the typical type Ⅰ, immunoglobulin (Ig) E (IgE) antibody-mediated, hypersensitive response of the nasal mucosa to environmental allergens for all age groups[41]. Allergic rhinitis and asthma are pathologically similar, and mucosal inflammation including the production of inflammatory factors (cytokines, adhesion molecules and inflammatory mediators) in allergic rhinitis is similar to that associated with bronchial asthma. In addition, allergic rhinitis is an independent risk factor for the development of asthma[41,42]. *H. pylori* is not always detectable in the nasal secretions of patients with gastric *H. pylori*[43] (Table 1), yet an inverse association between *H. pylori* infection and allergic rhinitis has been reported. An investigation into the association between the prevalence of *H. pylori* and pollinosis symptoms in healthy volunteers and the relationship between serum *H. pylori*-IgG and specific IgE antibodies for pollen, mites and house dust in 211 consecutive patients concluded that *H. pylori* infection might play an important role in protecting against the development of pollinosis, especially among younger patients[44]. The findings of a cross-sectional analysis of data from 7412 participants in the National Health and Nutrition Examination Survey 1999-2000 similarly showed that *H. pylori* seropositivity is inversely related to recent wheezing, allergic rhinitis, and dermatitis, eczema, or rash[37]. One possible explanation for these findings is the hygiene hypothesis[45]. Although definitive mechanisms remain unknown and contradictory opinions have been published[46,47], a protective role of *H. pylori* against allergic disorders including allergic rhinitis and asthma is biologically plausible.

Non-allergic rhinitis is also known as idiopathic, irritant-induced, and vasomotor rhinitis. Non-allergic rhinitis is a heterogeneous condition that has been classified in

Table 2 Detection of *Helicobacter pylori* in investigations of relationships between *Helicobacter pylori* and adenoiditis/adenoid hyperplasia

Ref.	Patients (*n*)	Samples	Methods	Positive results
Unver *et al*[73]	12	Adenoid tissue	Urease test	25%
Khademi *et al*[74]	56	Adenotonsillar tissue	Urease test	48%
Farhadi *et al*[75]	40	Adenoid tissue	PCR	15%
		Blood	ELISA (IgG)	20%
			ELISA (IgA)	17.5%
Eyigor *et al*[76]	47	Adenotonsillar tissue	Urease test	5.5%
			PCR	0%
Cirak *et al*[77]	10	Adenoid tissue	PCR	30%
Abdel-Monem *et al*[80]	10	Adenoid tissue	Urease test	40%
			PCR	20%
		Blood	ELISA	20%
Bulut *et al*[81]	71	Adenotonsillar tissue	Urease test	13.6%
			PCR	24.6%
Vilarinho *et al*[82]	55	Adenoid tissue	Urease test	3.6%
			IHC	0%
			FISH	0%
			PCR	0%
Hussey *et al*[83]	78	Adenoid tissue	PCR	0%
			Histology	0%
Vayisoglu *et al*[84]	60	Adenoid tissue	Urease test	3.3%
			IHC	3.3%
		Blood	ELISA (IgG)	13.3%
			ELISA (IgA)	3.3%
Bitar *et al*[85]	25	Adenoid tissue	Urease test	84%
			Histology	16%
			PCR	0%
Bitar *et al*[86]	18	Adenoid tissue	Urease test	72.2%
			PCR	0%
Pitkäranta *et al*[87]	20	Adenoid tissue	Culture	0%
		Fecal samples	ELISA	20%
Toros *et al*[88]	84	Adenoid tissue	Urease test	0%
			Histology	0%
Ozcan *et al*[89]	19	Adenoid tissue	Urease test	0%
			IHC	0%
Fancy *et al*[90]	45	Adenoid tissue	PCR	22.2%
Yilmaz *et al*[91]	42	Adenoid tissue	Culture	28.6%
			PCR	47.6%
Yilmaz *et al*[92]	38	Adenoid tissue	PCR	2.6%
Agirdir *et al*[93]	30	Adenoid tissue	Urease test	33.3%
Park *et al*[96]	62	Adenoid tissue	PCR	14.5%

ELISA: Enzyme-linked immunosorbent assay; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry; PCR: Polymerase chain reaction.

many ways. Because of the complexity of pathophysiological mechanisms in non-allergic rhinitis, this condition remains undefined and consensus regarding a management strategy has not been reached[48]. To the best of our knowledge, the relationship between non-allergic rhinitis and *H. pylori* and the role of *H. pylori* in acute rhinitis have never been investigated.

SINUSITIS

Chronic rhinosinusitis is defined as a persistent inflammatory response involving the mucous membranes of the nasal cavity and paranasal sinuses. It is usually diagnosed based on having at least two of the following characteristic symptoms: nasal congestion, facial pain/pressure, anterior or posterior nasal drainage, reduced or no sense of smell and persisting for > 12 wk, together with objective evidence of sinus disease determined by direct visualization or imaging[49-51].

H. pylori and the *cagA* gene have frequently been detected in nasal polyp specimens and the inflamed mucosa of the paranasal sinus in patients with chronic rhinosinusitis[52-58] (Table 1). *H. pylori* might play a positive role in chronic rhinosinusitis[59,60]. The prevalence of sinonasal *H. pylori* is higher in patients with, than without chronic rhinosinusitis[61,62]. Recent functional endoscopic sinus surgery for patients with chronic rhinosinusitis revealed that postoperative endoscopic scores improved significantly more among patients with chronic rhinosinusitis and *H. pylori* sinonasal colonization[63].

Contradictory opinions regarding the role of *H. pylori* in chronic rhinosinusitis have also been published. Ozcan *et al*[64] reported that infection with *H. pylori* is only transient, and that such infection could not possibly be an etiological factor for nasal polyposis. Furthermore, Lund-MacKay computed tomography and symptom scores did not indicate a significant correlation between intranasal *H. pylori* colonization and the preoperative severity of chronic rhinosinusitis[62].

Gastro-esophageal reflux might play a role in the pathogenesis of chronic rhinosinusitis[65-70]. Although pepsin/pepsinogen has been detected in sinonasal samples[71], others did not find a significant association between *H. pylori* in nasal polyps and nasal polyposis in patients without signs or symptoms of GERD[72]. These findings suggest that gastric juice infected with *H. pylori* and not *H. pylori* itself is involved in the development of chronic rhinosinusitis.

Chronic as well as allergic fungal rhinosinusitis can exist with or without nasal polyps, and sinusitis also includes acute rhinosinusitis[49,50]. Further studies are needed to identify the roles of *H. pylori* in the etiology of each subtype of sinusitis.

ADENOIDITIS AND ADENOID HYPERPLASIA

Adenoiditis is acute or chronic inflammation of the pharyngeal tonsils (adenoids). Adenoid hypertrophy, also termed adenoid hyperplasia or enlarged adenoids, is the unusual, non-tumorous, growth of the adenoid tissue.

Early studies used the rapid urease test (also known as the campylobacter-like organism test; CLO test) to detect *H. pylori* in adenoid tissues[73,74] (Table 2). Recent studies have applied the polymerase chain reaction (PCR) to detect *H. pylori* in adeno-tonsillar tissue specimens[75-77]. Exposure to an unsuitable environment can induce this organism to enter a viable but non-culturable state and to persist in the environment until it enters a suitable host[78,79]. Because of the characteristics, culturing the *H. pylori* organism from the samples of upper respiratory tract can be difficult, and thus can have low sensitivity[80].

Table 3 Detection of *Helicobacter pylori* in clinical investigations of relationships between *Helicobacter pylori* and otitis media

Ref.	Patients (*n*)	Samples	Methods	Positive results
Bitar *et al*[86]	28	Middle ear fluid	Culture	0%
Pitkäranta *et al*[87]	20	Middle ear fluid	Culture	0%
Ozcan *et al*[89]	25	Middle ear fluid	Urease test	0%
		Blood	ELISA (IgG)	32%
			ELISA (IgA)	12%
Fancy *et al*[90]	45	Middle ear fluid	PCR	32%
Yilmaz *et al*[91]	22	Middle ear fluid	Culture	9%
			PCR	31.8%
		Middle ear mucosa	Culture	4.5%
			PCR	27.3%
Yilmaz *et al*[92]	18	Middle ear fluid	PCR	66.7%
Agirdir *et al*[93]	45	Middle ear fluid	Urease test	66.6%
Morinaka *et al*[94]	15	Middle ear fluid	Urease test	20%
			IHC	80%
Karlidag *et al*[95]	38	Middle ear fluid	PCR	16.3%
Park *et al*[96]	60	Middle ear fluid	Urease test	26.7%
			PCR	33.3%
Bai *et al*[97]	60	Middle ear fluid	PCR	40%
			Culture	11.7%
			Urease test	11.7%
Kutluhan *et al*[101]	38	Middle ear tissue	PCR	7.9%
Dagli *et al*[102]	41	Middle ear mucosa	Urease test	53.6%

ELISA: Enzyme-linked immunosorbent assay; IHC: Immunohistochemistry; PCR: Polymerase chain reaction.

A comparison of the sensitivity and specificity of the rapid urease test, PCR and blood serology to detect *H. pylori* in the adenotonsillar tissue of symptomatic children with chronic adenotonsillitis found that PCR is the most reliable method of detecting *H. pylori* infection[80].

Several studies have detected *H. pylori* in adenoids and considered that the adenoids might serve as an ecological niche and as an extra-gastric reservoir for *H. pylori*[73-77,80,81]. However, contradictory opinions have also been expressed[82-84]. An analysis of 78 pediatric patients concluded that adenoid inflammation and enlargement are probably not due to ongoing *H. pylori* infection[83]. In addition, some authors reported that *H. pylori* has a limited (if any) role in the process of adenoid disease[85-90]. The pathophysiological role of *H. pylori* in adenoid tissue remains controversial and a definitive relationship between *H. pylori* and adenoid disease has not been established.

OTITIS MEDIA

Adenoiditis and adenoid hyperplasia are related to otitis media. We searched the English literature and found 11 original research studies of human samples and one systemic review describing the relationship between *H. pylori* and otitis media with effusion[86,87,89-98] (Table 3). In addition, two clinical studies investigated *H. pylori* in patients with chronic otitis media, and two studies examined the role of *H. pylori* in experimental animal models of otitis media[99-102].

H. pylori was detected in middle ear effusions in 8 of 11 clinical studies of otitis media with effusion[90-97]. On the other hand, cultures of middle ear fluid were all negative for *H. pylori* and CLO test results were also negative in another study of middle ear effusions[86,87,89]. Because *H. pylori* is difficult to detect in culture, its presence in middle ear effusions of some, but not all, patients with otitis media with effusion might be assumed. The next issue is whether *H. pylori* plays a role in the etiology of otitis media with effusion. Agirdir *et al*[93] collected middle ear effusions from 30 pediatric patients with otitis media with effusion, and washed the middle ears of 15 age-matched patients without middle ear effusion. They detected *H. pylori* in 20 (66.6%) patients with otitis media with effusion, but not in washes of the middle ears of patients without middle ear effusion according to the CLO. A PCR-based study of aspiration samples collected from 60 adult patients showed that 24 (40%) were *H. pylori*-positive[97]. These findings suggest that *H. pylori* could be responsible for the etiopathogenesis of otitis media with effusion. However, the relationship between *H. pylori* and otitis media with effusion remains controversial.

The CLO test and nested PCR of middle ear tissue samples found that 53.6% and 7.9%, respectively, of patients with chronic otitis media were positive for *H. pylori*[101,102]. The role of *H. pylori* in chronic otitis media is presently under investigation.

Live *H. pylori* or physiological saline was added to the middle ear cavities of New Zealand white rabbits with histamine-induced otitis media. A further injection of live *H. pylori* induced accelerated inflammation in the middle ear compared with animals that had been injected with histamine[99]. Another study found that the direct injection of protein extracted from whole cell sonicates of *H. pylori* (American Type Culture Collection) into the middle ear of mice induced the up-regulation of inflammatory cytokines (macrophage migration inhibitory factor, macrophage inflammatory protein 2, interleukin-1β and tumor necrosis factor-α), as well as the severe proliferation of inflammatory cells in middle ear epithelium[100]. These findings suggest that *H. pylori* plays a role in the development of middle ear inflammation, even if the bacterium is not live.

Particularly among children, acute otitis media is a common disease that is most often caused by *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis*[103]. We could not find any publications in the English literature describing the relationship between *H. pylori* infection and acute otitis media.

ORAL DISEASES

Numerous authors have reported the presence[104-109] or absence[110-114] of *H. pylori* in the oral cavity, especially in dental plaque, which is formed by colonizing bacteria attempting to attach to the smooth surface of teeth[115-121] (Table 4). The prevalence of gastric *H. pylori* infection

Table 4 Detection of *Helicobacter pylori* in studies with large samples that investigated relationships between *Helicobacter pylori* and oral diseases

Ref.	Patients (*n*)	Samples	Methods	Positive results
Bernander *et al*[110]	94	Dental plaque	Culture	0%
Luman *et al*[113]	120	Saliva and dental plaque	Culture	0%
Chaudhry *et al*[118]	89	Dental plaque	PCR	51.6%
Butt *et al*[119]	178	Dental plaque	Urease test	100%
Sudhakar *et al*[121]	50	Dental plaque	Culture	10%
			Urease test	70%
Assumpção *et al*[126]	99	Dental plaque	PCR	72%
	93		Urease test	52%
Gao *et al*[127]	96	Dental plaque	PCR	82.3%
Fernández-Tilapa *et al*[143]	200	Saliva and dental plaque	PCR	17%
		Blood	ELISA	62%
Eskandari *et al*[144]	67	Dental plaque	PCR	5.9%
Karczewska *et al*[145]	329	Gingival pocket material	Culture	50%
			PCR	35%
Oshowo *et al*[150]	208	Dental plaque	PCR	7.2%
			Culture	0.9%
		Tongue scraping	PCR	0%
			Culture	0%
Gall-Troselj *et al*[174]	268	Tongue mucosa	PCR	16%
Suzuki *et al*[177]	326	Saliva	PCR	6.2%

ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction.

was significantly higher among 443 dyspeptic patients with dental plaque that was positive, than negative for *H. pylori*[122].

H. pylori usually spreads *via* the fecal-oral route, and possibly by the oral-oral route and the spread of contaminated secretions[31,79,123-125]. An investigation of *H. pylori* genotypes in saliva, dental plaques, stools and gastric biopsy samples from 300 patients found that the fecal-oral route was the main method of *H. pylori* transmission. Furthermore, the oral cavity might serve as a reservoir for *H. pylori* because the genotypes of *H. pylori* isolates from saliva, stomach and stool are similar[126-129]. Debate continues regarding whether or not the oral cavity is the major reservoir of *H. pylori* for gastric re-infection[130-139]. Although some investigators have reported that the oral cavity is the reservoir for *H. pylori*[140-151], insufficient evidence supports the notion that dental treatment can prevent recurrent gastric *H. pylori* infection[152].

Aphthous stomatitis is the most common oral mucosal disease that causes small ulcers in the mouth, usually inside the lips, on the cheeks, or on the tongue and *H. pylori* might be an important factor in the recurrence of this condition[153-158]. However, conflicting findings have been reported[159-166]. A study of 36 consecutive patients affected by minor and major forms of recurrent aphthous stomatitis and 48 healthy volunteers found that *H. pylori* is not involved in recurrent aphthous stomatitis[167]. A recent systematic review has also shown that the pathogenesis of recurrent aphthous stomatitis and *H. pylori* are not associated[168].

A relationship with *H. pylori* has been investigated among various oral disorders including periodontal disease[169-173], glossitis, burning mouth syndrome[174], halitosis[175-177], Behçet's syndrome[178], lichen planus[179,180], and taste perception[181]. Combining periodontal with systemic therapy might be a promising approach to improving therapeutic effects and decreasing the risk of recurrent gastric infection[182]. However, an association between *H. pylori* and various periodontal disorders has not been established.

H. pylori might comprise part of the normal oral microflora[105]. *H. pylori* in dental plaque might not be associated with brushing frequency and oral health status and one study of 161 patients concluded that *H. pylori* is not pathogenic in the oral cavity[183-185].

In conclusion, whether or not *H. pylori* in the oral cavity plays a pathogenic role remains debatable. Nonetheless, dentists and dental professionals are at increased risk of exposure to *H. pylori* through contact with the oral cavities of infected patients[186,187].

TONSILLITIS AND TONSIL HYPERTROPHY

Chronic tonsillitis is a common condition characterized by persistent inflammation of the palatine tonsils, and bacterial infection is usually the cause. Idiopathic tonsillar hypertrophy presents without a history of infection and sometimes leads to obstructive sleep apnea and dysphagia.

H. pylori is detectable in tonsillar tissues and viable *H. pylori* can colonize these tissues[188-193] (Table 5). In addition, *H. pylori* has been identified in both tonsillar surface and core tissues[194,195]. A histopathological assessment of tonsillar tissues found that 130 (39.6%) of 285 children were positive for *H. pylori* and that the rapid urease test was not sensitive enough as a diagnostic tool[191]. A single method alone might not be sufficiently reliable to detect *H. pylori* in the tonsils, and thus, a combination of diagnostic methods could be recommended[196].

The rate of *H. pylori* infection was significantly higher in tonsillar tissues from a group of patients with tonsillitis compared with a group who had sleep-related breathing disorders (48% *vs* 24%)[197]. In contrast, another study found no significant difference between the incidence of *H. pylori*-positive tonsillar samples from patients with chronic tonsillitis and those with obstructive sleep apnea syndrome (80% *vs* 83%)[193]. Regardless, the high incidence of *H. pylori* infection in tonsil tissue indicates that tonsillectomy might impact gastric infection with this bacterium. A multiple regression analysis of confounding variables in patients with *H. pylori* gastric infection revealed that a history of tonsillectomy is associated with a decreased prevalence of gastric *H. pylori*[198]. In contrast, another report indicated that tonsillar tissue does not seem to be a reservoir for *H. pylori* infection and that tonsillectomy does not significantly affect gastric *H. pylori* eradication; however, the results might have been skewed by a relatively small sample size[199]. A comparison of genotypes between oropharyngeal and gastric *H. pylori*

Table 5 Detection of *Helicobacter pylori* in clinical investigations of relationships between *Helicobacter pylori* and tonsillitis/tonsil hypertrophy

Ref.	Patients (*n*)	Samples	Methods	Positive results
Unver *et al*[73]	16	Tonsillar tissue	Urease test	62.5%
Cirak *et al*[77]	22	Tonsillar tissue	PCR	18.2%
Abdel-Monem *et al*[80]	20	Tonsillar tissue	Urease test	60%
			PCR	15%
		Blood	ELISA	20%
Najafipour *et al*[188]	103	Tonsillar tissue	Urease test	48.5%
			PCR	19.4%
Farivar *et al*[189]	103	Tonsillar tissue	PCR	21.4%
			Histology	18.4%
Jabbari	285	Tonsillar tissue	Histology	39.6%
Moghaddam *et al*[191]			Urease test	14.0%
		Blood	ELISA	5.2%
Wibawa *et al* [192]	19	Tonsillar tissue	Culture	15.7%
Nártová *et al*[193]	89	Tonsillar tissue	PCR	80.9%
Khademi *et al*[194]	55	Adenotonsillar tissue	Urease test	82%
Aslan *et al*[195]	52	Tonsil core tissue	Urease test	47%
		Mucosal tissue	Urease test	42%
		Tonsillar tissue	Histology	0%
Lin *et al*[197]	94	Tonsillar tissue	Urease test	35%
Kusano *et al*[201]	173	Tonsillar tissue	IHC	72.8%
Kusano *et al*[202]	55	Tonsillar tissue	IHC	78.2%
Yilmaz *et al*[203]	50	Blood	ELISA	56%
		Stool	ELISA	50%
		Tonsillar tissue	Urease test	0%
Skinner *et al*[204]	50	Blood	ELISA	28%
		Tonsillar tissue	Urease test	0%
Jelavic *et al*[205]	77	Blood	ELISA	79%
		Tonsillar tissue	Urease test	12%
di Bonaventura *et al*[206]	72	Tonsillar swab	Culture	0%
			IHC	0%
Di Bonaventura *et al*[207]	72	Tonsillar tissue	PCR	0%

ELISA: Enzyme-linked immunosorbent assay; IHC: Immunohistochemistry; PCR: Polymerase chain reaction.

isolates from six patients revealed important differences within each individual[200]. Although the sample size was very small, these findings suggest that tonsils do not comprise a reservoir for gastric *H. pylori* infection, and that more than one *H. pylori* strain can exist in the oropharynx and stomach of the same patient.

Coccoid *H. pylori* isolated from the tonsillar tissues of patients with IgA nephropathy is one causative antigen of this disease[201,202]. A relationship between *H. pylori* and acute tonsillitis has not been reported.

Although a possible role for *H. pylori* residing in the tonsils has been indicated, other studies have not detected *H. pylori* in specimens of adenotonsillectomy, and have not found that tonsillar tissues constitute a reservoir for *H. pylori* infection[203-207]. The disparity might be due to a difference in sample populations and methodology.

PHARYNGEAL DISEASES

Acute or chronic pharyngitis is defined as inflammation of the mucous membranes and submucosal tissues of the pharynx. The main symptom of pharyngitis is a sore throat. Several factors including nasal obstruction, chronic sinonasal infection, allergy, smoking, chronic periodontal infections, polluted air, industrial fumes, excessively hot or cold foods and alcohol consumption are associated with pharyngeal inflammation[208]. Gastroesophageal reflux is also considered an important factor in pharyngeal disorders[209,210], and *H. pylori* residing in the pharynx might play a role in the development of pharyngitis. Some studies have tested this hypothesis by examining an association between *H. pylori* and pharyngitis (Table 6).

Table 6 Detection of *Helicobacter pylori* in investigations of relationships between *Helicobacter pylori* and benign pharyngeal/laryngeal diseases

Ref.	Patients (*n*)	Samples	Methods	Positive results
Pharyngeal disease				
Aladag *et al*[208]	41	Blood	ELISA	78%
Zhang *et al*[211]	50	Pharyngeal tissue	Histology	38%
Kaptan *et al*[212]	70	Pharyngeal tissue	PCR	27.1%
			Culture	5.8%
Elsheikh *et al*[213]	146	Pharyngeal tissue	PCR	32.9%
Laryngeal disease				
Ozyurt *et al*[52]	27	Laryngeal tissue	PCR	58.6%
Burduk *et al*[58]	30	Laryngeal tissue	PCR	100%
Cekin *et al*[215]	43	Laryngeal tissue	PCR	55.8%
Youssef *et al*[217]	212	Stool	ELISA	57.5%
Rubin *et al*[222]	101	Blood	ELISA	54.5%
Talaat *et al*[223]	162	Stool	ELISA	86.4%
Tiba M *et al*[224]	14	Laryngeal tissue	PCR	71.4%
			IHC	71.4%
Borkowski *et al*[226]	35	Laryngeal tissue	Urease test	17.1%
Siupsinskiene *et al*[227]	54	Laryngeal tissue	Urease test	37.0%
Jaspersen *et al*[228]	38	Gastric tissue	Urease test	36.8%
		Laryngeal swab	Culture	0%

ELISA: Enzyme-linked immunosorbent assay; IHC: Immunohistochemistry; PCR: Polymerase chain reaction.

A prospective study of 50 patients with chronic pharyngitis found that none of the control group had *H. pylori* in the pharynx, whereas 19 (38.0%) in the group with pharyngitis were *H. pylori*-positive in template-directed dye-terminator assays with fluorescence polarization detection[211]. One study of 70 patients with chronic pharyngitis and 20 healthy controls using PCR and cultures to detect *H. pylori* colonization in pharynx mucous membranes found that none of the controls had *H. pylori* in the pharynx and that chronic nonspecific pharyngitis without gastric *H. pylori* infection was significantly related to *H. pylori* colonization in the pharynx[212]. They concluded that chronic pharyngitis might be associated with *H. pylori* infection and that gastric involvement increases the rate of pharyngeal colonization by *H. pylori*.

Another study identified a possible relationship between the prevalence of *H. pylori* DNA and recurrent aphthous ulcerations in mucosa-associated lymphoid tissues of the pharynx[213]. Acute pharyngitis is usually caused by bacterial or viral infection. To the best of our

Table 7 Detection of *Helicobacter pylori* in investigations of relationships between *Helicobacter pylori* and head and neck malignancies

Ref.	Patients (*n*)	Samples	Methods	Positive results
Siupsinskiene *et al*[227]	13	Laryngeal tissue	Urease test	46.2%
Shi *et al*[230]	59	Laryngeal tissue	PCR	76.3%
Aygenc *et al*[231]	26	Blood	ELISA	73.1%
Okuda *et al*[232]	58	Oral swab	PCR	100%
Burduk[233]	80	Laryngeal tissue	Urease test	62.5%
Dayama *et al*[234]	20	Oral tissue	Culture	15%
			PCR	15%
Rubin *et al*[235]	53	Blood	ELISA	64.2%
Rezaii *et al*[236]	98	Blood	ELISA	93.9%
Gong *et al*[237]	81	Laryngeal tissue	PCR	71.6%
		Blood	ELISA	77.8%
Grimm *et al*[238]	191	Oral tissue	IHC	21.5%
Kizilay *et al*[241]	69	Laryngeal tissue	Histology	0%
Akbayir *et al*[242]	50	Laryngeal tissue	IHC	0%
Pirzadeh *et al*[243]	65	Laryngeal tissue	Urease test	0%
			Histology	0%
Kanda *et al*[244]	31	Laryngeal tissue	PCR	0%
			Culture	0%
			IHC	0%
		Urine	ELISA	67.7%
Grandis *et al*[245]	21	Blood	ELISA	57%
Nurgalieva *et al*[246]	119	Blood	ELISA	32.8%
Lukeš *et al*[248]	11	Oropharyngeal lymphoid tissue	Culture	9.1%
	23	Oropharyngeal lymphoid tissue	PCR	73.9%
	41	Blood	ELISA	78.1%
Pavlík *et al*[249]	3	Blood	ELISA	0%
		Tonsillar tissue	PCR	100%

ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction.

knowledge, a causative role of *H. pylori* in acute pharyngitis has never been reported. The etiological role of *H. pylori* in pharyngeal diseases remains obscure. Further studies are needed to understand the pathogenic role of *H. pylori* in the pharynx.

LARYNGEAL DISEASES

The impact of gastric juice with low pH on laryngeal disorders has been reported[214]. Both laryngopharyngeal and gastroesophageal reflux might cause laryngopharyngeal symptoms, and laryngopharyngeal reflux has been identified in 50.4% (57/113) of patients with laryngeal and voice disorders[215-221]. Laryngopharyngeal reflux is involved in the pathogenesis of several laryngeal disorders, including chronic posterior laryngitis, vocal fold nodules, paroxysmal laryngospasm, Reinke's edema, laryngeal true vocal fold ulcers and granuloma as well as globus sensation[216].

The larynx could be directly exposed to *H. pylori* as a result of pharyngolaryngeal reflux, and gastric *H. pylori* infection might be associated with disorders of the larynx[52,222] (Table 6). One study found more prevalent *H. pylori* infection among 162 patients who presented mainly with chronic, persistent cough of unidentifiable causes compared with controls and that the eradication of *H. pylori* significantly improved patient symptomatology[223]. Another study found that patients with minimal vocal fold lesions (vocal fold polyps and nodules, and posterior granulomas) were commonly positive for *H. pylori* and that its eradication should be considered when presented with such lesions[224]. A PCR study detected *H. pylori* DNA (*ureA* gene) in samples from all of 30 patients with benign larynx diseases (polyps and Reinke's edema) and the *H. pylori cagA* gene was identified in 7 (23.3%) of them[58].

Laryngitis is inflammation of the larynx due to various factors[225]. Some clinical studies have shown a possible role for *H. pylori* in the etiology of chronic laryngitis[226,227]. The positive rates of *H. pylori* in laryngeal samples from patients with vocal cord polyps and laryngitis were significantly higher than the rate in control samples (32.0% and 45.5% *vs* 9.1%)[227]. In contrast, others have found no evidence to support the notion that *H. pylori* is associated with laryngitis and rather suggested that acid reflux was the underlying etiology[228].

Presumably *H. pylori* is detectable in some laryngeal diseases. However, whether *H. pylori* plays an etiological role in the larynx has not been established due to the paucity and reliability of published studies.

HEAD AND NECK CANCER

H. pylori infection causes chronic gastritis and peptic ulceration and it is the strongest risk factor for the development of gastric and colorectal cancers[8,9]. *H. pylori* might also be related to other cancers. Some epidemiological studies have shown that the odds ratios (estimated relative risks) of lung cancer with *H. pylori* infection range from 1.24 to 17.78 compared with controls, suggesting an increased risk of lung cancer in populations exposed to *H. pylori* infection, although a causal relationship between *H. pylori* and lung cancer has not been confirmed[229]. However, evidence regarding the role of *H. pylori* infection in gastrointestinal carcinogenesis suggests a relationship between *H. pylori* and malignancies of the head and neck[227].

Several investigators have identified *H. pylori* in patients with head and neck malignancies[230-232] (Table 7). Inflammation induced by *H. pylori* would cause epithelial cell proliferation that could develop into laryngeal cancer[233]. A pilot study uncovered a possible association between *H. pylori* and an increased risk of oral cancer, and another study detected *H. pylori* antibodies in serum samples from 34 (64.2%) of 53 patients with head and neck squamous cell carcinoma (larynx, hypopharynx, tongue, tonsil, nasopharynx, and tongue base/vallecula)[234,235]. Multivariate regression analyses in two case control studies identified *H. pylori* infection as an independent risk factor for laryngo-hypopharyngeal carcinoma[236,237]. A recent study of a large patient cohort associated immunohistochemically detected *H. pylori* expression in oral squamous cell carcinoma with reduced disease-free survival[238].

In contrast, others have not found *H. pylori* in head and neck cancers or in laryngeal carcinoma samples[239-243]. PCR, culture and immunohistochemical methods did not detect *H. pylori* in head and neck tumor tissues from 31 patients, even though 21 of them carried anti-*H. pylori* antibodies[244]. A statistically significant difference in the incidence of *H. pylori* seropositivity between patients with head and neck cancer and controls has not yet been reported and others have shown that *H. pylori* infection either protects against or promotes laryngopharyngeal carcinoma[245,246].

The presence of *H. pylori* in head and neck tumor tissues and/or the stomach of patients with head and neck malignancies might be widespread; however, more information is required about *H. pylori* activities in patients with head and neck carcinogenesis[247-249].

CONCLUSION

Epidemiological studies have shown that the prevalence of carrying *H. pylori* ranges from 10%-20% to 80%-90% in developed and developing countries, respectively, and most carriers are asymptomatic[250,251]. The findings of published studies on the impact of *H. pylori* on the upper respiratory tract are inconsistent. Whether or not *H. pylori* is located in the upper respiratory tract and whether or not it plays a role in the pathogenesis of upper respiratory tract diseases remain unresolved. The risks and benefits of *H. pylori* and its role in upper respiratory disorders including cancer require urgent assessment.

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