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Helicobacter pylori – Not Only a Gastric Pathogene?

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1. Introduction

Helicobacter pylori is a spiral, microaerophillic, Gram-negative bacterium. Infection by *H. pylori* has been established as the major cause of chronic gastritis and plays important role in the pathogenesis of other gastroduodenal diseases such as peptic ulceration, gastric lymphoma, and gastric cancer (Israel and Peek 2001). *H. pylori* is considered to be the most common chronic bacterial infection in humans (Cave 1996). The prevalence has been estimated to range from 40 to 80% and it varies widely by geographic area, age, race, ethnicity, and socioeconomic status (Bures et al. 2006). In most cases the infection is silent, clinical manifestation appears in only 10-15% of infected individuals. This is due to different strength of virulence of *H. pylori* strains and different host immune system response (Stromberg et al. 2003).

The stomach was supposed to be the only reservoir of infection in humans. Nevertheless *H. pylori* infection was detected in other sites recently. It was found in dental plaque and saliva (Kim et al. 2000) and also in oropharyngeal lymphatic tissue (Pavlik et al. 2007). This finding is of great importance because of known carcinogenic potential of *H. pylori*. It was declared type I carcinogen by IARC (1994). The question of direct contribution of *H. pylori* to oral and oropharyngeal diseases was not resolved yet.

2. *H. pylori* pathogenesis

Immunological changes caused by *H. pylori* in the stomach mucosa were explained recently (Tummala et al. 2004). There are no more detailed data about effect of *H. pylori* in the oral or oropharyngeal mucosa. *H. pylori* has several mechanisms to elude host defences (Portal-Celhay and Perez-Perez 2006). It is able to survive the acidic gastric environment by producing the enzyme urease, which metabolizes urea to carbon dioxide and ammonia to

buffer the gastric acid. *H. pylori* moves across gastric mucus and can adhere to epithelial cells using a variety of adhesin-like proteins (Sachs et al. 2003). Once adhered to epithelial cells, *H. pylori* induces a strong immune system response (Crabtree 1996). This response does not lead to elimination of the bacterium, but causes development of chronic inflammation. *H. pylori* is not eradicated unless an infected individual is treated with a combination of antibiotics (Portal-Celhay and Perez-Perez 2006). Chemical products of *H. pylori* attract cells of the immune system into lamina propria (Blanchard et al. 2004). It was shown that *H. pylori* can induce the maturation and activation of monocyte-derived dendritic cells. This activity is mediated by TLRs (Toll-like receptors) expressed on antigen presenting cells and leads to promotion of NK and Th1 effector responses (Portal-Celhay and Perez-Perez 2006). IFN – gamma producing Th1 polarized T cells and activated NK cells have been suggested to play an important role for development of severe pathologies (Hafsi et al. 2004).

H. pylori infection in gastric mucosa is associated with the production of both proinflammatory and immunomodulatory cytokines. Changes in secretion of IL-8, IL-1beta, IL-6, TNF-alpha, TGF-beta were described (Stromberg et al. 2003). These cytokines are produced by both the immune system and epithelial cells. The response of host cells is dependent on production of *H. pylori* virulence factors (Blanchard et al. 2004). The most important virulence factors, which are associated with gastric diseases, are CagA (cytotoxin associated gene A) and VacA (vacuolizating cytotoxin A).

3. *H. pylori* virulence factors

Genome sequence analysis led to identification of genes encoding these virulence factors grouped in the so-called pathogenicity island (cagPAI). It is a genomic region containing about 30 genes including genes for type IV secretion system (Mobley 1996). *H. pylori* strains producing CagA are associated with increased risk of severe gastric pathologies compared with CagA negative strains (Portal-Celhay and Perez-Perez 2006). Injection of bacterial proteins into the gastric cells by a type IV bacterial secretion system (a multi-molecular complex that mediates the translocation of bacterial factors into the host cell) has been described (Segal et al. 1999; Oliveira et al. 2006). In this way, CagA protein can get inside the host cells and stimulate cell signalling through interaction with several host proteins. This interaction leads to increased cytokine and regulatory molecule production (Guillemin et al. 2002) and could be related to initiation of tumour transformation (Segal 1997; Tummala et al. 2004; Hatakeyama 2006).

VacA is another important *H. pylori* virulence factor. This bacterial toxin with multiple activities is inserted into the host cell membrane, inducing cytoplasmic vacuolation (Cover and Blaser 1992). This toxin is coded by *vacA* gene, which is present in all *H. pylori* strains. Only about 50% of strains produce VacA protein. This is due to variability of *vacA* sequence. (Portal-Celhay and Perez-Perez 2006). There are several types of signal region (s1a, s1b, s1c, s2) and two types of midregion (m1 or m2). *H. pylori* strains with different forms of *vacA* differ in association with diseases. Strains with s1 signal sequence allele produce intact VacA toxin, s2 strains have low cytotoxic activity. Strains with s1/m1 allele combination have highest cytotoxic activity and they are associated with gastric ulceration and gastric carcinoma (Miehlke et al. 2000). s1/m2 strains are characterized by medium or low VacA production and s2/m2 strains do not produce VacA at all (Van Doorn et al. 1999). s2/m1 strains was found only sporadically (Letley et al. 1999; Martinez-Gomis et al. 2006).

Other virulence factors are e.g. adhesins, which help *H. pylori* to adhere to mucosal epithelial cells (Gisbert and Pajares 2004). Important is BabA protein which binds Lewis^b antigen, which is present in individuals with 0 blood group. Presence of *BabA* gene is connected to increased prevalence of gastric ulcers and gastric carcinoma in Lewis^b positive individuals (Blanchard et al. 2004). *BabA* often coexists with *vacA* s1 and *cagA* alleles (Kusters et al. 2006).

4. *H. pylori* induced carcinogenesis

H. pylori is a declared type I carcinogen (IARC, 1994). However, the exact way of carcinogenesis is not yet fully understood. There are three supposed ways of *H. pylori* carcinogenic action:

1. *H. pylori* could act as direct mutagen. Interaction of intracellular signalling molecules and *H. pylori* CagA may predispose cells to accumulate multiple genetic and epigenetic changes that promote multistep carcinogenesis (Hatakeyama 2006).
2. *H. pylori* produced VacA can cause immunosuppression by blocking proliferation of T cells (Boncristiano et al. 2003),
3. *H. pylori* can induce cell proliferation by increasing levels of several cytokines and regulatory molecules, which are involved in tumour formation and cell transformation (Konturek et al. 1997; Sakaguchi et al. 1999; Keates et al. 2001; Gobert et al. 2002; Schiemann et al. 2002; Wang et al. 2002). Current information about regulation mechanism of epithelial tissue by cytokines and regulatory molecules focus an interest mainly on Epithelial Growth Factor (EGF), Transforming Growth Factor (TGF) and NO synthases (NOS) (Gallo et al. 1998; Rubin Grandis et al. 1998; Sakaguchi et al. 1999; Gobert et al. 2002; Schiemann et al. 2002).

5. Methods of *H. pylori* detection in the oral cavity and pharynx

Diagnostics of *H. pylori* is significantly developed in gastroenterology. Attempts of *H. pylori* detection in other sites encountered diverse success rates (Dowsett and Kowolik 2003). Routinely used tests can be divided into non-invasive and invasive group. When detecting extragastric presence of *H. pylori*, invasive tests must be used based on the detection of bacteria in biopsy specimen. These invasive tests are often used to detect extragastric *H. pylori* presence:

Histology – Several staining methods are in use. These include e.g. haematoxylin and eosin, modified Giemsa, Warthin Starry, Gimenez, and Genta (Rotimi et al., 2000). These staining methods achieve high sensitivity and specificity rates (up to 96%) (Hep 2003) in case of gastric mucosa specimens, where no other bacterial strains are supposed to be present, but provide low specificity in the case of oral specimens, where other bacterial strains are often found (Dowsett and Kowolik, 2003). Differentiation of *H. pylori* from other bacteria can be very difficult.

Rapid Urease Test (RUT) or Campylobacter-like Organism (CLO) test is based on detection of urease production by *H. pylori*. When viable *H. pylori* bacteria are present, urea is being cleaved and the change of pH is visualized by colour indicator (Qureshi et al. 1992). This is very useful method when dealing with gastric mucosa specimens, in case of other specimens results may show high false-positive rate because of some other urease-producing species presence, e.g. *Streptococcus spp., Haemophilus spp.* a *Actinomyces spp.* (Dowsett and Kowolik 2003).

Culture is currently accepted gold standard for the diagnosis of gastric *H. pylori* (Makristathis et al., 2004). This method achieve 80-90% sensitivity and 90-100% specificity rates (Hep 2003). Culture of *H. pylori* from the oral cavity or oropharynx showed to by highly difficult to perform and has met with limited success (Dowsett and Kowolik, 2003). Use of special transport medium, microaerophilic environment, supplemented media for culture and three to seven days incubation is mandatory. Overgrowth by other bacterial species often appears. Direct inhibition of *H. pylori* by oral species in vitro has also been reported (Ishihara et al., 1997). Transformation of *H. pylori* into unculturable, coccoid form in the unfavourable environment was described (Shahamat et al., 2004).
Immunohistochemistry – to detect extragastric *H. pylori* is being used only experimentally. Tissue sections are incubated with rabbit polyclonal anti-*H. pylori* antibodies followed with the use of streptavidin-biotin-peroxidase kit and haematoxylin and eosin counterstaining (Akbayir et al. 2005).
Molecular methods – are currently generating most possibilities of detection and also typing of *H. pylori* strains. Various modifications of the polymerase chain reaction (PCR) are in use. These methods are used only for experimental purposes in the detection of extragastric *H. pylori*. In experiments on the detection of oral and pharyngeal *H. pylori* many variations of PCR diagnosis has been used with a detection rate ranging between 0-90% (Dowsett and Kowolik 2003). The lack of uniformity of laboratory procedures can play a role in the reported inconsistencies. The described modification exerted different primers and probes for the detection of different DNA segments of *H. pylori* DNA. Various primers were used (for example, urease gene, 16S ribosomal RNA genes and others). Specificity and sensitivity of different primers, however, can vary significantly (Song et al., 1999). PCR genotyping makes it possible to distinguish different *H. pylori* strains and their carriage of genes encoding virulence factors (Pavlik et al. 2007). The discrepancy of published PCR results shows the importance of finding suitable PCR assay. Tissue specimens collection and especially immediate immersion into proper transport medium is essential for successful test results (Pavlik et al. 2007). It has to be considered that PCR allows the detection of a low number of bacteria or nonviable bacteria, which cannot influence progress of diseases.

6. *H. pylori* in oropharyngeal lymphatic tissue

Several studies have explored the presence of *H. pylori* in tonsillar and adenoid tissue. The results of these studies were inconsistent with different detection rates. The discrepancies are due to different detection methods used. Some of the methods are believed to be unsuitable for detection of extragastric *H. pylori* (e.g. RUT or CLO test). PCR assay is now considered the most appropriate method for detection of pharyngeal *H. pylori*. However, differences in the primers and probes used in published studies do not allow drawing specific conclusions. Table 1. shows an overview of published papers focused on the detection of *H. pylori* in tonsillar and adenoid tissue. According to above mentioned data PCR assay is considered most valuable detection method for extragastric *H. pylori* detection. In their study Di Bonaventura et al. (2001) used PCR for investigation of tonsillar swabs and biopsy specimens with no evidence of *H. pylori* presence. Cirak et al. (2003), Bulut et al. (2006) found *H. pylori* in tonsillar and adenoid tissue by PCR (*16S rRNA* gene and *glmM* gene respectively). They found *H. pylori* strains positive for *cagA* gene. Bitar et al. (2005) investigated adenoid tissue specimens by RUT, histology and nested PCR (*ureA* gene). They found positivity by RUT and histology, but no positivity by nested PCR. In their next study

these authors investigated middle ear fluids and adenoid tissue specimens using culture, RUT and PCR (*ureC* and adhesion subunit genes). All middle ear fluids were negative. In adenoids they found positivity by RUT, but none by PCR (Bitar et al. 2006). Yilmaz et al. (2004) found *H. pylori* in middle ear effusions and in one adenoid tissue specimen using PCR (*23S rRNA* gene). Yilmaz et al. (2006) found *H. pylori* in 64% of adenoid and tonsillar specimens by PCR (*16S rRNA* gene). Kusano et al. (2007) showed *H. pylori* positivity in 126 (72.9%) tonsillar specimens using PCR (*16S rRNA* gene). They also demonstrated the presence of coccoid forms of *H. pylori* in tonsillar crypts using immunoelectron microscopy. Eyigor et al. (2009) found 5,5% of adenoid and tonsillar specimens positive for *H. pylori* by RUT, but none of them positive by PCR (*glmM* gene). Vilarinho et al. (2010) found 3 adenoid and tonsillar specimens positive by RUT, 2 positive by immunohistochemistry, but none positive by fluorescence in situ hybridization or PCR (*vacA* gene). Abdel-Monem (2011) found 16 (53.3%) adenoid and tonsillar specimens positive by RUT and 5 (16.6%) specimens positive by PCR (*ureC* gene). Other studies mentioned in Table 1. used different diagnostic methods with different detection rates.

The relationship between *H. pylori* infection and gastric tumour pathogenesis has been well described. It was supposed that *H. pylori* could act the same way in progression of oropharyngeal tumourigenesis. Some authors tried to identify a correlation between *H. pylori* and cancers of head and neck (Table 2.). Tests which determined serum levels of anti-*H. pylori* antibodies in patients with head and neck spinocellular carcinoma (HNSCC) brought inconsistent results (Grandis et al. 1997; Aygenc et al. 2001; Rubin et al. 2003; Nurgalieva et al. 2005). Okuda et al. (2000) proved the presence of *H. pylori* in oral swab specimens and oral cancer specimens using RT PCR (reverse transcriptase polymerase chain reaction) and culture. On the other hand Kanda (2005) found no HNSCC specimen positive using PCR, culture and immunohistochemical analysis. Kizilay et al. (2006) did not find *H. pylori* in laryngeal SCC and non-neoplastic specimens using haematoxylin and eosin stain or modified Giemsa stain. Akbayir et al. (2005) found *H. pylori* in specimens collected from laryngeal cancers and benign laryngeal disorders by histopathological methods, but not by immunohistochemical methods. Only one study performed PCR genotyping of *H. pylori* strains in specimens collected from the oropharynx. Tonsillar tissue specimens were collected from patients with chronic tonsillitis, obstructive sleep apnea syndrome (OSAS) and tonsillar cancer. The detected *H. pylori* strains differ from strains found in the stomachs of Czech patients with gastric diseases (Pavlik et al. 2007).

7. Comparison of oral and oropharyngeal genotypes

It is supposed that *H. pylori* is spread from person to person by oral-oral or faecal-oral route (Brown 2000), this hypothesis has not yet been convincingly demonstrated. Assuming the oral cavity and oropharynx as a gateway of infection, we can assume that in the oral cavity and oropharynx of the same individual we can find *H. pylori* strains of the same genotype. Initial works focused on comparison of oral and gastric *H. pylori* strains used endonuklease restriction analysis, single strand conformation polymorphism analysis (SSCP) or PCR (Shames et al. 1989; Khandaker et al. 1993; Zhang and Lu 1997; Kim et al. 2003). Identical strains have been found in gastric mucosa and oral cavity. The first comparison of gastric and oral *H. pylori* strains using PCR genotyping performed Wang et al. (2002) and, consequently, Burgers et al. (2008). Different genotypes in the stomach and oral cavity were found in both studies. PCR assays used by these authors could be considered more accurate

Author	Year	Subjects	Specimens	Diagnostic Method	Number of Subjects positive for *H.pylori*
Di Bonaventura	2000	36	tonsillar swabs	culture, imunohistochemistry	0 (0%)
Di Bonaventura	2001	75	tonsillar swabs and biopsy	PCR	0 (0%)
Unver et al.	2001	19	adenoid tissue	CLO test	11 (58%)
Skinner et al.	2001	50	tonsillar tissue	CLO test, imunocytochemistry	0 (0%) CLO test and imunocytochem.
Uygur-Bayramicli	2002	27	tonsillar tissue	histology, imunohistochemistry	0 (0%) histology and imunohistochemistry
Cirak	2003	23	tonsillar and adenoid tissue	PCR (16S ribosomal RNA, CagA)	7 (30%) positive for *H. pylori*
					5 of them (71%) positive for Cag A gene
Yilmaz et al.	2004	50	tonsillar and adenoid tissue	CLO test	0 (0%)
Yilmaz et al.	2005	38	adenoid tissue,	PCR (23S ribosomal RNA)	12 (67%) in middle ear effusion.
			middle ear effusions		1 (5%) in adenoid tissue
Pitkaranta	2005	20	adenoid tissue and middle ear fluid	culture	0 (0%)
Khademi et al.	2005	56	tonsillar and adenoid tissue	CLO test	27 (48%)
Bitar	2005	25	adenoid tissue	RUT, histology and nested PCR	21 (84%) positive by RUT,
				(UreA)	4 (16%) positive by histology
					0 (0%) positive by nested PCR
Bulut	2006	71	tonsillar and adenoid tissue	PCR (CagA - glmM gene)	29 (24,6%) postitive for *H. pylori*
					17 of them (58,6%) CagA positive
Bitar	2006	28	adenoid tissue and middle ear	culture, RUT, PCR (urease-C,	0 (0%) middle ear fluids
			fluid	adhesion subunit genes)	10 (77%) adenoid tissue by RUT
					0 (0%) by PCR
Yilmaz et al.	2006	22	middle ear fluid, promontorium	culture, PCR (16S RNA)	middle ear fluids: 2 positive by culture,
			mucosa,adenoid and tonsillar		7 by PCR
			tissue		mucosa: 1 by culture, 7 by PCR
					adenoids 11 (50%) by culture,
					14 (64%) by PCR
					tonsillar tissue:12 (55%) by culture,
					14 (64% by PCR)
Kusano et al.	2007	173	palatal tonsils	immunohistochemistry,	126 (72,9%) positive
				immunoelectron microscopy,	
				in-situ hybridization,	
				PCR (16S RNA gene)	
Vayisoglu et al.	2008	91	tonsillar and adenoid tissue	RUT, immunohistochemistry	2 (2,2%) adenoid tissue,
					0 (0%) tonsillar tissue using RUT,
					0(0%) immunohostochemistry
Eyigor et al.	2009	55	35 adenoids, 20 tonsils	RUT, PCR (glmM gene)	RUT 5,5% positive,
					0% PCR positive
Ozcan	2009	25	adenoid tissue, middle ear fluid	CLO, immunohistochemistry	0 (0%) CLO positive,
					0 (0%) immunohistochemistry positive
Jabbari Moghaddam	2009	285	tonsillar tissue	RUT, histopathology	113 (39.6%) positive by histopatology
					40 (14%) positive by RUT
Vilarinho et al.	2010	62	adenoid and tonsillar tissue	RUT, immunohistochemistry,	3 positive by RUT,
				fluorescence in situ hybridization	2 positive by immunohistochemistry,
				(FISH), PCR-DNA hybridization	0 positive by FISH,
				assay (vacA gene)	0 positive by PCR
Abdel-Monem	2011	20	adenoid and tonsillar tissue	RUT, PCR (ureC gene)	16 (53.3%) positive by RUT,
					5 (16.6%) positive by PCR

Table 1. Studies focused on detection of pharyngeal presence of *H. pylori*

Author	Year	Subjects	Specimens	Diagnostic Method	Number of Subjects Positive for *H. pylori*
Grandis et al.	1997	42	21 SCC	serology - IgG antibodies	57% with SCC
			21 controls without SCC		62% controls
Okuda et al.	2000	116	116 gastric and oral samples	RT-PCR, culture	46,6% gastric samples
			including 58 oral cancers		12,1% oral swab samples
					100% oral cancer swabs
Aygenc et al.	2001	58	26 laryngeal SCC	serology - IgG antibodies	73% with SCC
			32 controls without SCC		41% controls
Rubin et al.	2003	61	6 severe laryngeal dysplasia,	serology	38 seropositive (including all tonsillar SCC)
			5 tonsillar SCC, 50 other SCC		
Akbayir et al	2005	100	50 laryngeal SCC	histopathological and	0 (0%) imunihist.
			50 benign laryngeal disorders	imunohistochemical methods	28 SCC, 1 benign by histol.
Kanda et al.	2005	31	31 SCC	PCR, culture, immunohistochemical	21 seropositive
				analysis, serology - from urine	0 PCR, culture , immunohist.
Nurgalieva et al.	2005	230	119 laryngeal or pharyngeal SCC	serology - IgG antibodies	32,8% with SCC
			111 controls without SCC		27,0% controls
Kizilay et al.	2006	99	69 laryngeal SCC	histology - HE, modified Giemsa stain	0%
			30 nonneoplastic controls		
Pavlik et al.	2006	7	3 chronic tonsillitis	serology IgA, IgG, IgM	2 of 3 chronic tonsillitis serolgicaly
			3 tonsillar SCC	PCR genotyping	2 of 3 chronic tonsillitis, 3 of 3 SCC and 1 of 1
			1 OSAS		OSAS by PCR

Table 2. Studies focused on possible role of *H. pylori* in head and neck carcinogenesis

(Schabereiter-Gurtner et al. 2004). Findings of Lukes et al. (2009) are in concordance with these results. In four of six individuals different genotypes of *H. pylori* strains were found in the stomach and oropharynx. The results also show that from 20 individuals with proven

oropharyngeal *H. pylori* infection, only 8 had concurrent gastric infection. This confirms the findings of Burgers et al. (2008), who report that only 38% of persons with demonstrated presence of *H. pylori* in the oral cavity also had the infection in the stomach. These authors also reported the finding of 10 cases with positive *H. pylori* in saliva, with no detectable specific anti-*H. pylori* antibodies in serum. This is consistent with the results obtained by Lukes et. al. (2009). *H. pylori* was found in the oropharynx in 12 patients with no demonstrable antibody response.

8. Conclusions

Oral cavity (saliva and dental plaque) is now considered a possible extragastric reservoir of *H. pylori*. The published works dealing with oropharyngeal and nasopharyngeal detection of *H. pylori* infection have yielded contradictory results. Pharyngeal detection of *H. pylori* was reported in the range of 0-90%. Regarding that the various authors used different methods of detection, it is not possible to reach valuable conclusions. Frequently used tests like CLO test and RUT appears to be inappropriate methods for diagnosis of pharyngeal *H. pylori*. The presence of other urease-producing bacterial strains in the pharynx can lead to false positive results. Culture has proved to be very difficult and not very resistant to external influences, which may even prevent a successful detection. Molecular diagnostics (PCR) can be regarded as a method with sufficient sensitivity and specificity. Results achieved by these methods demonstrated the presence of *H. pylori* in the lymphoid tissue of oropharynx and nasopharynx. PCR method allows not only detect the presence of *H. pylori* infection, but also genotyping of strains within the tissue. The fact remains that the PCR methods allow determine the presence of bacterial DNA but can not determine whether the DNA comes from live or dead bacteria. Results of culture despite the very low numbers of positive results indicate the possible presence of viable bacteria capable of reproduction. High susceptibility of *H. pylori* in adverse effects during transport of specimens or during handling in the laboratory can explain low numbers of positive results of culture. Also, a frequent colonisation of oropharyngeal tissue by other bacterial species can have a significant influence on the failure of the culture of *H. pylori.*

The assumption that the oropharyngeal *H. pylori* infection may contribute to oropharyngeal carcinogenesis as a direct mutagen was not confirmed yet. An analogous situation, however, occurs in the stomach, where prevalence of *H. pylori* infection among the population is reported between 40-80%, serious stomach problems such as gastroduodenal ulcer disease or gastric cancer has only 10 -15% of infected.

Virulence of *H. pylori* strains varies according to the production of toxins. This production is due to the presence of virulence factor genes. Most important are the *cagA* gene and *vacA* gene. The main carcinogenic effect of *H. pylori* is declared to be associated with the presence of *cagA* gene and s1/m1 combination of alleles of *vacA* gene. Recent studies indicate that *H. pylori* may exist in the oropharynx independently to the gastric infection. Comparison of genotypes of *H. pylori* in the oral cavity, oropharynx, and stomach showed that an individual can host more than one strain of *H. pylori* in various locations. Differences were found in the presence of *cagA* gene and in the structure of *vacA* gene.

The findings of *H. pylori* in the oral cavity and oropharynx without demonstrable specific anti-*H. pylori* antibodies in serum are remarkable. This could be explained by an early detection of *H. pylori* presence after primary infection, when the antibody response has not started yet. Next, the possibility that *H. pylori* could colonize the oral cavity and the

oropharynx without inducing the host immune response must be considered. Another possible explanation is the presence of *H. pylori* coccoid forms. These are viable form of bacteria that can not be cultivated by conventional microbiological techniques and are characterized by a reduced virulence.

The question of transmission of *H. pylori* has not been satisfactorily resolved yet. If we consider the oral-oral or faecal-oral route as a way of transmission, we can assume finding of the same *H. pylori* strains in the oropharynx and stomach in the same individual. The findings of different genotypes in both locations still lack an accurate explanation. Inoculation of mixtures of *H. pylori* strains and consequently their different settlements in the different areas according to sensitivity of the strains could be one of the possible explanations. It can be assumed that the area of the oropharynx is less favourable for *H. pylori*, and can only be colonized by more resistant strains. One of the negative factors for growth and reproduction of *H. pylori* is the presence of other bacterial strains that were able to stop the growth of *H. pylori* during in-vitro experiments. A variety of bacterial colonization in the oral cavity and oropharynx can be assumed.

Epidemiological data on the prevalence of *H. pylori* infection published in the literature are often based on serological detection of specific anti-*H. pylori* antibodies. The prevalence of infection is reported 40-80%. The presence of anti-*H. pylori* antibodies was given in relation only to gastric infection. The newly obtained data prove the possibility of the presence of *H. pylori* infection in other locations independently to the gastric infection. This should be considered in future epidemiological studies. Not only antibodies should be evaluated but also identification of the exact location of the infection must be done.

In the future it would be appropriate to focus attention on local effects of *H. pylori* in oropharyngeal lymphoid tissue. Changes in the expression of some cytokines caused by *H. pylori*, which were described in the gastric mucosa, can be expected in the oropharyngeal tissue. Another study focused on oropharyngeal *H. pylori* genotyping should be done. In case that high virulent *H. pylori* strains can survive in oropharyngeal tissue, translocation of toxins into the oropharyngeal mucosa cells with subsequent cytokine response can be expected. Nevertheless this assumption has not been confirmed nor refuted yet.

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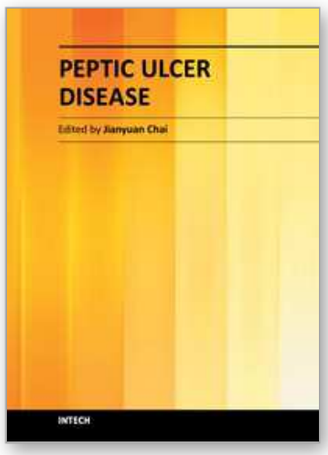

Peptic Ulcer Disease

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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