Chapter from the book *Peptic Ulcer Disease*

Downloaded from: http://www.intechopen.com/books/peptic-ulcer-disease

Interested in publishing with InTechOpen?
Contact us at book.department@intechopen.com
**Helicobacter pylori – Not Only a Gastric Pathogene?**

Petr Lukes¹, Jaromir Astl¹, Emil Pavlik², Bela Potuznikova², Jan Plzak¹-³, Martin Chovanec¹-³ and Jan Betka¹

¹Charles University in Prague, 1st Faculty of Medicine, Department of Otorhinolaryngology and Head and Neck Surgery, Faculty Hospital Motol, Prague
²Charles University in Prague, 1st Faculty of Medicine, Institute of Immunology and Microbiology, Prague
³Charles University in Prague, 1st Faculty of Medicine, Institute of Anatomy, Prague
Czech Republic

### 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. \textit{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, \textit{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. \textit{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 \textit{H. pylori} attract cells of the immune system into lamina propria (Blanchard et al. 2004). It was shown that \textit{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). \textit{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 \textit{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 (vacuolizing cytotoxin A).

3. \textit{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). \textit{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).

\textit{VacA} is another important \textit{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 \textit{vacA} gene, which is present in all \textit{H. pylori} strains. Only about 50% of strains produce VacA protein. This is due to variability of \textit{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). \textit{H. pylori} strains with different forms of \textit{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\textsuperscript{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\textsuperscript{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 be 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 endonuclease 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.
Peptic Ulcer Disease

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* |
|--------------------|------|----------|----------------------------|---------------------------------------------|-------------------------------------------|
| Di Bonaventura     | 2000 | 36       | tonsillar swabs            | culture, immunohistochemistry               | 0%                                        |
| Di Bonaventura     | 2001 | 75       | tonsillar swabs and biopsy | PCR                                         | 0%                                        |
| Guert et al.       | 2001 | 19       | adenoid tissue             | CLO test                                    | 11 (61%)                                  |
| Slommer et al.     | 2001 | 50       | tonsillar tissue           | CLO test, immunochemistry                    | 0% (24%)                                  |
| Uygur-Bayramci     | 2002 | 27       | tonsillar tissue           | Histology, immunohistochemistry             | 0% (20%)                                  |
| Cifrá              | 2003 | 23       | tonsillar and adenoid tissue | PCR (16S ribosomal RNA, CagA) | 7 (30%) positive for *H. pylori* |
| Yilmaz et al.      | 2004 | 50       | tonsillar and adenoid tissue | CLO test                                    | 0%                                        |
| Yilmaz et al.      | 2005 | 38       | adenoid tissue             | PCR (23S ribosomal RNA)                      | 12 (31%) in middle ear effusion. |
| Gümür et al.       | 2005 | 20       | adenoid tissue and middle ear fluid | culture                                    | 0%                                        |
| Khademi et al.     | 2005 | 56       | tonsillar and adenoid tissue | CLO test                                    | 27 (48%)                                  |
| Bilis              | 2005 | 25       | adenoid tissue             | RUT, histology and nested PCR               | 21 (84%) positive by RUT, (UreA)         |
| Buatu              | 2006 | 71       | tonsillar and adenoid tissue | PCR (CagA - glmM gene)                      | 29 (41.3%) positive for *H. pylori*     |
| Bilis              | 2006 | 28       | adenoid tissue and middle ear fluid | culture, RUT, PCR (urease-C, fluid adhesion subunit genes) | 0% (0%) middle ear fluids |
| Yilmaz et al.      | 2006 | 22       | middle ear fluid, promontonum mucosa, adenoid and tonsillar tissue | culture, PCR (16S RNA)  | middle ear fluids: 2 positive by culture, |
| Kusano et al.      | 2007 | 173      | palatal tonsils            | Immunohistochemistry,                         | 126 (72.9%) positive               |
| Vayssoglu et al.   | 2008 | 91       | tonsillar and adenoid tissue | RUT, immunohistochemistry                    | 2 (2.2%) adenoid tissue,               |
| Eyigor et al.      | 2009 | 55       | 35 adenoids, 20 tonsils    | RUT, PCR (glmM gene)                        | 5 (9.1%) positive, 0%                  |
| Ozcan              | 2009 | 25       | adenoid tissue, middle ear fluid | PCR                                          | 0% (0%) CagA positive                  |
| Jabbari Moghaddam  | 2009 | 285      | tonsillar tissue           | RUT, histopathology                         | 113 (39.6%) positive by histopathology |
| Vlaminrh et al.    | 2010 | 62       | adenoid and tonsillar tissue | RUT, immunohistochemistry,                   | 4 positive by RUT,                       |
| Abd-El-Monem       | 2011 | 29       | adenoid and tonsillar tissue | RUT, PCR (ureC gene)                        | 16 (53.3%) positive by RUT,            |

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.

### 9. Acknowledgements

This work was supported by grant NT11523 of the Internal Grant Agency of the Ministry of Health of the Czech Republic

### 10. References

Abdel-Monem MH, Magdy EA, Nour YA, Harfoush RA, Ibreak A (2011) Detection of Helicobacter pylori in adenotonsillar tissue of children with chronic adenotonsillitis using rapid urease test, PCR and blood serology: A prospective study. Int J Pediatr Otorhinolaryngol

Akbayir N, Basak T, Seven H, Sungun A, Erdem L (2005) Investigation of Helicobacter pylori colonization in laryngeal neoplasia. Eur Arch Otorhinolaryngol 262:170-172.

Ayגנכ E, Selcuk A, Celikkanat Ş, Ozbek C, Ozdem C (2001) The role of Helicobacter pylori infection in the cause of squamous cell carcinoma of the larynx. Otolaryngol Head Neck Surg 125:520-521.
Bitar M, Mahfouz R, Soweid A, Racoubian E, Ghasham M, Zaatar G, Fuleihan N (2006) Does Helicobacter pylori colonize the nasopharynx of children and contribute to their middle ear disease? Acta Otolaryngol 126:154-159.

Bitar MA, Soweid A, Mahfouz R, Zaatar G, Fuleihan N (2005) Is Helicobacter pylori really present in the adenoids of children? Eur Arch Otorhinolaryngol 262:987-992.

Blanchard TG, Drakes ML, Czinn SJ (2004) Helicobacter infection: pathogenesis. Curr Opin Gastroenterol 20:10-15.

Boncristiano M, Paccani SR, Barone S, Ulivieri C, Patrussi L, Illver D, Amedei A, D’Elios MM, Telford JL, Baldari CT (2003) The Helicobacter pylori vacuolating toxin inhibits T cell activation by two independent mechanisms. J Exp Med 198:1887-1897.

Brown LM (2000) Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 22:283-297.

Bulut Y, Agacayak A, Karlidag T, ToramanZA, Yilmaz M (2006) Association of cagA+ Helicobacter pylori with adenotonsillar hypertrophy. Tohoku J Exp Med 209:229-233.

Bures J, Kopacova M, Koupi I, Vorisek V, Rejchrt S, Beranek M, Seifert B, Pozler O, Zivny P, Douda T, Kolesarova M, Pinter M, Palicka V, Holcik J (2006) Epidemiology of Helicobacter pylori infection in the Czech Republic. Helicobacter 11:56-65.

Burgers R, Schneider-Brachert W, Reischl U, Behr A, Hiller KA, Lehn N, Schmalz G, Ruhl S (2008) Helicobacter pylori in human oral cavity and stomach. Eur J Oral Sci 116:297-304.

Cave DR (1996) Transmission and epidemiology of Helicobacter pylori. Am J Med 100:12S-17S; discussion 17S-18S.

Cirak MY, Ozdek A, Yilmaz D, Bayiz U, Samim E, Turet S (2003) Detection of Helicobacter pylori and its CagA gene in tonsil and adenoid tissues by PCR. Arch Otolaryngol Head Neck Surg 129:1225-1229.

Cover TL, Blaser MJ (1992) Purification and characterization of the vacuolating toxin from Helicobacter pylori. J Biol Chem 267:10570-10575.

Crabtree JE (1996) Immune and inflammatory responses to Helicobacter pylori infection. Scand J Gastroenterol Suppl 215:3-10.

Di Bonaventura G (2001) Do tonsils represent an extragastric reservoir for Helicobacter pylori infection. J Infect 42(3):221-222.

Dowsett SA, Kowolik MJ (2003) Oral Helicobacter pylori: can we stomach it? Crit Rev Oral Biol Med 14:226-233.

Eyigor M, Eyigor H, Gultekin B, Aydin N (2009) Detection of Helicobacter pylori in adenotonsillar tissue specimens by rapid urease test and polymerase chain reaction. Eur Arch Otorhinolaryngol 266:1611-1613.

Gallo O, Masini E, Morbidelli L, Franchi A, Fini-Storchi I, Vergari WA, Ziche M (1998) Role of nitric oxide in angiogenesis and tumor progression in head and neck cancer. J Natl Cancer Inst 90:587-596.

Gisbert JP, Pajares JM (2004) Review article: C-urea breath test in the diagnosis of Helicobacter pylori infection – a critical review. Aliment Pharmacol Ther 20:1001-1017.

Gobert AP, Mersey BD, Cheng Y, Blumberg DR, Newton JC, Wilson KT (2002) Cutting edge: urease release by Helicobacter pylori stimulates macrophage inducible nitric oxide synthase. J Immunol 168:6002-6006.
Grandis JR, Perez-Perez GI, Yu VL, Johnson JT, Blaser MJ (1997) Lack of serologic evidence for Helicobacter pylori infection in head and neck cancer. Head Neck 19:216-218.

Guillemin K, Salama NR, Tompkins LS, Falkow S (2002) Cag pathogenicity island-specific responses of gastric epithelial cells to Helicobacter pylori infection. Proc Natl Acad Sci U S A 99:15136-15141.

Hafsi N, Voland P, Schwendyl S, Rad R, Reinl W, Gerhard M, Prinz C (2004) Human dendritic cells respond to Helicobacter pylori, promoting NK cell and Th1-effector responses in vitro. J Immunol 173:1249-1257.

Hatakeyama M (2006) The role of Helicobacter pylori CagA in gastric carcinogenesis. Int J Hematol 84:301-308.

Hep A (2003) Současné možnosti diagnostiky Helicobacter pylori. MEDICÍNA PO PROMOCI 4:6-8.

IARC (1994) Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum 61:1-241.

Israel DA, Peek RM (2001) pathogenesis of Helicobacter pylori-induced gastric inflammation. Aliment Pharmacol Ther 15:1271-1290.

Kanda T (2005) Investigation of Helicobacter pylori tumor tissue specimens from patients of head and neck tumor. Practica Oto-Rhino-Laryngologica 98:571-575.

Keates S, Sougioultzis S, Keates AC, Zhao D, Peek RM, Jr., Shaw LM, Kelly CP (2001) cag+ Helicobacter pylori induce transactivation of the epidermal growth factor receptor in AGS gastric epithelial cells. J Biol Chem 276:48127-48134.

Khandaker K, Palmer KR, Eastwood MA, Scott AC, Desai M, Owen RJ (1993) DNA fingerprints of Helicobacter pylori from mouth and antrum of patients with chronic ulcer dyspepsia. Lancet 342:751.

Kim JM, Kim JS, Jung HC, Oh YK, Chung HY, Lee CH, Song IS (2003) Helicobacter pylori infection activates NF-kappaB signaling pathway to induce iNOS and protect human gastric epithelial cells from apoptosis. Am J Physiol Gastrointest Liver Physiol 285:G1171-1180.

Kim N, Lim SH, Lee KH, You JY, Kim JM, Lee NR, Jung HC, Song IS, Kim CY (2000) Helicobacter pylori in dental plaque and saliva. Korean J Intern Med 15:187-194.

Kizilay A, Saydam L, Aydin A, Kalcioğlu MT, Ozturan O, Aydin NE (2006) Histopathologic examination for Helicobacter pylori as a possible etiopathogenic factor in laryngeal carcinoma. Chemotherapy 52:80-82.

Konturek PC, Ernst H, Konturek SJ, Bobrzyński AJ, Faller G, Klingler C, Hahn EG (1997) Mucosal expression and luminal release of epidermal and transforming growth factors in patients with duodenal ulcer before and after eradication of Helicobacter pylori. Gut 40:463-469.

Kusano K, Tokunaga O, Ando T, Inokuchi A (2007) Helicobacter pylori in the palatine tonsils of patients with IgA nephropathy compared with those of patients with recurrent pharyngotonsillitis. Hum Pathol 38:1788-1797.

Kusters JG, van Vliet AH, Kuipers EJ (2006) Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 19:449-490.

Letley DP, Lastovica A, Louw JA, Hawkey CJ, Atherton JC (1999) Allelic diversity of the Helicobacter pylori vacuolating cytotoxin gene in South Africa: rarity of the vacA
s1a genotype and natural occurrence of an s2/m1 allele. J Clin Microbiol 37:1203-1205.

Lukes P, Pavlik E, Potuznikova B, Plzak J, Nartova E, Dosedel J, Katra R, Sterzl I, Betka J, Astl J (2009) Comparison of Helicobacter pylori genotypes obtained from the oropharynx and stomach of the same individuals. Unpublished manuscript.

Martinez-Gomis J, Diouf A, Lakhssassi N, Sixou M (2006) Absence of Helicobacter pylori in the oral cavity of 10 non-dyspeptic subjects demonstrated by real-time polymerase chain reaction. Oral Microbiol Immunol 21:407-410.

Miehlke S, Kirsch C, Agha-Amiri K, Gunther T, Lehn N, Malferttheiner P, Stolte M, Ehninger G, Bayerdorffer E (2000) The Helicobacter pylori vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. Int J Cancer 87:322-327.

Mobley HL (1996) Defining Helicobacter pylori as a pathogen: strain heterogeneity and virulence. Am J Med 100:25S-95S; discussion 95S-115S.

Nurgalieva ZZ, Graham DY, Dahlstrom KR, Wei Q, Sturgis EM (2005) A pilot study of Helicobacter pylori infection and risk of laryngopharyngeal cancer. Head Neck 27:22-27.

Okuda K, Ishihara K, Miura T, Katakura A, Noma H, Ebihara Y (2000) Helicobacter pylori may have only a transient presence in the oral cavity and on the surface of oral cancer. Microbiol Immunol 44:385-388.

Oliveira MJ, Costa AC, Costa AM, Henriques L, Suriano G, Atherton JC, Machado JC, Carneiro F, Seruca R, Mareel M, Leroy A, Figueiredo C (2006) Helicobacter pylori induces gastric epithelial cell invasion in a c-Met and type IV secretion system-dependent manner. J Biol Chem 281:34888-34896.

Pavlik E, Lukes P, Potuznikova B, Astl J, Hrda P, Soucek A, Matucha P, Dosedel J, Sterzl I (2007) Helicobacter pylori isolated from patients with tonsillar cancer or tonsillitis chronica could be of different genotype compared to isolates from gastrointestinal tract. Folia Microbiol (Praha) 52:91-94.

Portal-Celhay C, Perez-Perez GI (2006) Immune responses to Helicobacter pylori colonization: mechanisms and clinical outcomes. Clin Sci (Lond) 110:305-314.

Qureshi H, Ahmed W, Zuberi SJ, Kazi J (1992) Use of CLO test in the detection of Helicobacter pylori infection and its correlation with histologic gastritis. J Pak Med Assoc 42:292-293.

Rubin Grandis J, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MM, Drenning SD, Tewardy DJ (1998) Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst 90:824-832.

Rubin JS, Benjamin E, Prior A, Lavy J (2003) The prevalence of Helicobacter pylori infection in malignant and premalignant conditions of the head and neck. J Laryngol Otol 117:118-121.

Sachs G, Weeks DL, Melchers K, Scott DR (2003) The gastric biology of Helicobacter pylori. Annu Rev Physiol 65:349-369.

Sakaguchi AA, Miura S, Takeuchi T, Hokari R, Mizumori M, Yoshida H, Higuchi H, Mori M, Kimura H, Suzuki H, Ishii H (1999) Increased expression of inducible nitric oxide synthase and peroxynitrite in Helicobacter pylori gastric ulcer. Free Radic Biol Med 27:781-789.

Segal ED (1997) Consequences of attachment of Helicobacter pylori to gastric cells. Biomed Pharmacother 51:5-12.
Peptic Ulcer Disease

Segal ED, Cha J, Lo J, Falkow S, Tompkins LS (1999) Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by Helicobacter pylori. Proc Natl Acad Sci U S A 96:14559-14564.

Shames B, Krajden S, Fukasa M, Babida C, Penner JL (1989) Evidence for the occurrence of the same strain of Campylobacter pylori in the stomach and dental plaque. J Clin Microbiol 27:2849-2850.

Schabereiter-Gurtner C, Hirschl AM, Dragosics B, Huffnagl P, Puz S, Kovach Z, Rotter M, Makristathis A (2004) Novel real-time PCR assay for detection of Helicobacter pylori infection and simultaneous clarithromycin susceptibility testing of stool and biopsy specimens. J Clin Microbiol 42:4512-4518.

Schiemann U, Konturek J, Assert R, Rembiasz K, Domschke W, Konturek S, Pfeiffer A (2002) mRNA expression of EGF receptor ligands in atrophic gastritis before and after Helicobacter pylori eradication. Med Sci Monit 8:CR53-58.

Stromberg E, Edebo A, Svennerholm AM, Lindholm C (2003) Decreased epithelial cytokine responses in the duodenal mucosa of Helicobacter pylori-infected duodenal ulcer patients. Clin Diagn Lab Immunol 10:116-124.

Tummala S, Keates S, Kelly CP (2004) Update on the immunologic basis of Helicobacter pylori gastritis. Curr Opin Gastroenterol 20:592-597.

Van Doorn LJ, Figueiredo C, Megraud F, Pena S, Midolo P, Queiroz DM, Carneiro F, Vanderborght B, Pegado MD, Sanna R, De Boer W, Schneeberger PM, Correa P, Ng EK, Atherton J, Blaser MJ, Quint WG (1999) Geographic distribution of vacA allelic types of Helicobacter pylori. Gastroenterology 116:823-830.

Vilarinho S, Guimaraes NM, Ferreira RM, Gomes B, Wen X, Vieira MJ, Carneiro F, Godinho T, Figueiredo C (2010) Helicobacter pylori colonization of the adenotonsillar tissue: fact or fiction? Int J Pediatr Otorhinolaryngol 74:807-811.

Wang J, Chi DS, Laffan JJ, Li C, Ferguson DA, Jr., Litchfield P, Thomas E (2002) Comparison of cytotoxin genotypes of Helicobacter pylori in stomach and saliva. Dig Dis Sci 47:1850-1856.

Yilmaz M, Kara CO, Kaleli I, Demir M, Tumkaya F, Buks AS, Topuz B (2004) Are tonsils a reservoir for Helicobacter pylori infection in children? Int J Pediatr Otorhinolaryngol 68:307-310.

Yilmaz T, Ceylan M, Akyon Y, Ozcakyr O, Gursel B (2006) Helicobacter pylori: a possible association with otitis media with effusion. Otolaryngol Head Neck Surg 134:772-777.

Zhang Y, Lu X (1997) [Detection and differentiation of Helicobacter pylori from gastric biopsy and saliva by PCR-SSCP]. Zhonghua Nei Ke Za Zhi 36:446-449.
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.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Petr Lukes, Jaromir Astl, Emil Pavlik, Bela Potuznikova, Jan Plzak, Martin Chovanec and Jan Betka (2011). Helicobacter pylori – Not Only a Gastric Pathogene?, Peptic Ulcer Disease, Dr. Jianyuan Chai (Ed.), ISBN: 978-953-307-976-9, InTech, Available from: http://www.intechopen.com/books/peptic-ulcer-disease/helicobacter-pylori-not-only-a-gastric-pathogene-