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1 **Epidemiology, Diagnosis and Risk factors of *Helicobacter pylori***
2 **infection**

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15 **Key words:** Prevalence, invasive and non-invasive methods, familial factors, environment,
16 life habits

1 **Abstract**

2 *Helicobacter pylori* is a human-specific pathogen which leads to gastric pathologies including
3 gastric cancer. It is a highly unique bacterium considered as a carcinogenic agent. *H. pylori*
4 remains a major human health problem, responsible for ~90% of the gastric cancer cases. Ap-
5 proximately four billion individuals have been detected for *H. pylori* infection worldwide in
6 2015. At the turn of the 21st century, the prevalence of *H. pylori* has been declining in highly
7 industrialized countries of the Western world, whereas prevalence has plateaued at a high
8 level in developing and newly industrialized countries. However, the infection status remains
9 high in immigrants coming from countries with high prevalence of *H. pylori* infection.
10 *H. pylori* can be diagnosed by invasive and non-invasive methods. Urea breath test and stool
11 antigens detection are among the most commonly used non-invasive ones. Although the way
12 *H. pylori* is transmitted remains still unclear, the level of contamination is strongly dependent
13 on the familial and environmental context, with a drastic impact of living conditions with
14 poor hygiene and sanitation. However, familial socioeconomic status is the main risk factor
15 for *H. pylori* infection among children. In addition, food and water source have a high impact
16 on the prevalence of *H. pylori* infection worldwide. This chapter highlights the latest
17 knowledge in the epidemiology of *H. pylori* infection, its diagnosis and critical risk factors
18 responsible for its high prevalence in some populations and geographic areas.

1 **1. Introduction**

2 *Helicobacter pylori* is a spiral-shaped and flagellated Gram-negative bacterium which
3 colonizes specifically the human stomach. *H. pylori* infects about 50% of the population
4 worldwide, making it the most widespread infection in humans, especially in developing
5 countries where its prevalence is estimated to be around 80% (Torres et al, 2000). *H. pylori*
6 infection leads to chronic gastritis, which can evolve either into peptic ulcer diseases or into
7 the development of pre-neoplastic lesions (intestinal metaplasia, dysplasia) and
8 adenocarcinoma (Correa 1992). It is until now, the only bacterium recognized as a type 1
9 carcinogenic agent (IARC, 1994). Persistent *H. pylori* colonization and the associated chronic
10 inflammation are critical parameters for the development of gastric malignancies. Further
11 knowledge on the epidemiology of the infection, its pathways of transmission and risk factors
12 could lead to public-health measures for the prevention and control of this infection. The
13 purpose of this chapter is to give an overview of the recent epidemiological data on the
14 prevalence of *H. pylori* infection among the world population and the available diagnostic
15 tools for its detection. The infection rate is known to be linked to socioeconomic factors.
16 However environmental factors including source of water and sanitary conditions as well as
17 factors related to food can also lead to the dissemination of *H. pylori* infection. An update of
18 these different risk factors will also be developed in this review.

19 **2. Epidemiology of *H. pylori* infection**

20 A recent review with reports from 62 countries estimates that more than half the world's po-
21 pulation is still infected with *H. pylori*. This means that, based on regional prevalence esti-
22 mates, there were approximately 4.4 billion individuals with *H. pylori* infection worldwide in
23 2015 with a wide variation in the prevalence of *H. pylori* between regions and countries. Pre-

1 valence is highest in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia
2 (54.7%). In contrast, *H. pylori* prevalence is lowest in Northern America (37.1%) and Oceania
3 (24.4%). At the turn of the 21st century, the prevalence of *H. pylori* has been declining in
4 highly industrialized countries of the Western world, whereas prevalence has plateaued at a
5 high level in developing and newly industrialized countries. The widening differential gap in
6 prevalence has important implication on the future worldwide prevalence of diseases asso-
7 ciated with *H. pylori*, including peptic ulcer and gastric cancer. These differences in *H. pylori*
8 prevalence likely reflect the level of urbanization, sanitation, access to clean water, and varied
9 socioeconomic status (Hooi et al. 2017). In children, a comprehensive review and meta-
10 analysis of original pediatric studies from 2011 to 2016 performed on healthy children esti-
11 mated an overall seroprevalence rate of 33% [95% confidence interval (CI) 27–38] (Zabala
12 Torres et al. 2017). In the same study, a review of information available from seven cohort
13 studies concluded that infection rates in healthy children under 5 years of age were still bet-
14 ween 20 and 40% in high-income countries and between 30 and 50% in upper-middle income
15 countries, indicating that the country of birth plays a role in infection prevalence. Higher rates
16 of infection (40%), as determined by cross-sectional studies, are predominantly seen in low or
17 low-to-middle-income areas (or in countries with severe income inequality). However, huge
18 variations in prevalence can be observed between countries with similar living conditions.
19 This can be observed in Europe, for example, where the prevalence of *H. pylori* infection re-
20 mains high in Spain and Portugal, although the levels of sanitation and of economic develop-
21 ment have risen in recent decades and are comparable to other European countries where the
22 prevalence of infection is significantly lower. Similar variations from country to country can
23 also be seen in Asia, which cannot be fully explained by only looking at the level of develop-
24 ment (Zamani et al. 2018). There are significant differences in the *H. pylori* prevalence even

1 within the same country. For example, different racial groups in the United States have diffe-
2 rent *H. pylori* prevalence. It was reported that the prevalence in non-Hispanic whites ranges
3 from 18.4% to 26.2% and that in non-whites ranges from 34.5% to 61.6% (Everhart et al.
4 2000; Cardenas et al. 2006).

5 The prevalence of *H. pylori* infection in both children and adults is, however, still decreasing
6 in developed countries. One study from Iceland involved 205 children aged 7–17 years and
7 found only 3.4% of infection (Asgeirsdottir et al. 2017). Furthermore, the prevalence was
8 2.6% among children when both parents were born in a low prevalence country compared
9 with 17% among those with at least one parent born in a high prevalence area ($p = 0.026$).
10 This confirms results obtained in Belgium some years ago (Mana et al. 2013). In Poland, the
11 prevalence of *H. pylori* infection in 8,661 symptomatic and untreated children from 2000 to
12 2013 assessed by culture was 16.1%. The highest prevalence of infection was found in the
13 year 2000 (23.1%) and the lowest in 2010 (8.9%) (Biernat et al. 2016). However, in Latvia,
14 no evidence of a fall in prevalence in children was found during the last 10 years and the pre-
15 valence determined by stool antigen test was 15.5% (Daugule et al. 2016).

16 The prevalence is also decreasing in some countries in Asia and in the Middle East. Indeed,
17 studies from Japan have shown a considerable fall in *H. pylori* prevalence in childhood. One
18 study from a high gastric cancer incidence area found only 85 of 1765 (4.8%) students aged
19 13–15 years to be infected (Kusano et al. 2017) and, in another study, the prevalence in
20 school children aged 12–15 years was 3.1% (Nakayama et al. 2017). The same fall has been
21 observed in Iran, where former reports of *H. pylori* infection rate indicated a global preva-
22 lence of more than 85% and recent ones estimated an overall prevalence of 54%, with a pre-
23 valence of 42% in children (Moosazadeh et al. 2016). Similar trends are seen in the chinese

1 city Hangzhou, where the infection rates in three age groups (3–6, 7–11, and 12–17 years)
2 were 14.8, 20.2, and 25.8%, respectively. The overall prevalence decreased from 21.6 to
3 17.2% between 2007 and 2014 (Shu et al. 2017). In contrast, in Vietnam, the seroprevalence
4 in 1,094 subjects from 278 households remained stable at 51.4% in adults and 41.4% in chil-
5 dren (Nguyen et al. 2016). Conversely, the prevalence of *H. pylori* infection remains high in
6 newly arrived refugees attending the migrant health service in South Australia, where 922
7 adults and children were screened in a cross-sectional study using a monoclonal stool antigen
8 test. *H. pylori* infection was detected in 198 of them (21.5%), almost 1.5 times that of the
9 Australian population's estimate when both adults and children are included (Abdul Rahim et
10 al. 2017). A systematic review involving 28 studies described the prevalence of *H. pylori*
11 among migrants. In all but two, the prevalence was similar to or lower than in their country of
12 origin but higher than in their country of destination. Second and later generations of migrants
13 had a lower prevalence than the first generation (Morais et al. 2017).

14 As mentioned above, *H. pylori* has been identified as a Group I carcinogen by the Internatio-
15 nal Agency for Research on Cancer (IARC 1994) and currently is considered as necessary,
16 but insufficient cause of gastric adenocarcinoma (Eslick et al. 1999; Uemura et al. 2001). Ap-
17 proximately 89% of all gastric cancers can be attributable to *H. pylori* infection. In Africa,
18 despite the high *H. pylori* prevalence, the reported incidence of gastric cancer was considera-
19 bly lower compared with China or Japan and was postulated to be related to the predominant
20 non-atrophic gastritis pattern in Africa; the archetypal *H. pylori Africa2* type strain largely
21 restricted in South Africa, which lacks the *cag* (cytotoxin-associated genes) pathogenicity
22 island; and lastly intestinal parasitic infestation modulating the immune response against *H.*
23 *pylori* toward a Th2 type response, which may reduce the risk of gastric cancer (Correa and
24 Piazzuelo 2011; Kodaman et al, 2014). The now defunct phenomenon known as “African

1 enigma” was attributed to the inadequate sampling of the African population obtained through
2 endoscopic data, limited access to health care, and a relatively short life expectancy in the po-
3 pulation. More recent and robust data on the African gastric ulcer and cancer prevalence con-
4 firmed that it is not as low as reported previously (Graham et al. 2009).

5 Ongoing efforts to monitor *H. pylori* prevalence and its disease burden in a systematic manner
6 is crucial, as it will minimize any skewed data, which can adversely affect the allocation of
7 health care resources.

8 **3. Diagnosis of *H. pylori* infection**

9 *H. pylori* infection can be confirmed by invasive methods, requiring gastric biopsies ob-
10 tained during an endoscopy (histology, culture, PCR: polymerase chain reaction, RAP: rapid
11 urease test) or non-invasive methods (SAT: stool antigen test, UBT: urea breath test, and se-
12 rology). The invasive tests are used in clinical practice and the non-invasive ones mostly in
13 epidemiology and to assess the outcome of an eradication treatment. It is necessary to have at
14 least two concordant tests to confirm or deny an infection in clinical practice (Fallone et al.
15 2016) (Malfertheiner et al. 2017; Jones et al. 2017). Indeed, false negative results of any di-
16 agnostic tests for *H. pylori* can occur since the sensitivity of any test never reaches 100% and
17 the sensitivity is lower in case of antimicrobial use within the previous 4 weeks, of proton
18 pump inhibitor within the previous 2 weeks or in case of Upper GI: gastrointestinal bleeding.
19 False-positives are rare, but can occur and when present may be due to the occurrence of oth-
20 er urease containing bacteria such as *Proteus mirabilis*, *Citrobacter freundii*, *Klebsiella*
21 *pneumoniae*, *Enterobacter cloacae* and *Staphylococcus aureus* (Osaki et al. 2008). Non-
22 invasive tests are also used in test and treat strategies, that should now be restricted to adults
23 living in high prevalence countries presenting dyspepsia without any alarm symptoms

1 (Fallone et al. 2016; Malfertheiner et al. 2017). However, the number of patients to treat suc-
2 cessfully to improve dyspepsia symptoms in one is around 12 (Moayyedi et al. 2006). In the
3 context of a prudent use of antibiotics, it may appear not justified to prescribe antibiotic which
4 will induce resistance to the drug in case of failure, be responsible of adverse events and have
5 a high cost (although the cost-effectiveness may vary according to the cost of care in a given
6 country).

7 **3.1 Histology**

8 Demonstration of the presence of *H. pylori* by histological analysis of gastric biopsies is faci-
9 litated by special stains such as Giemsa or immunohistochemical techniques (Lash and Genta
10 2016) using antibodies directed against surface antigens of the bacterium. This diagnostic
11 method remains the most commonly used and allows the gradation of gastritis: classification
12 of Sydney (Dixon et al. 1996) (Fig. 1), OLGA (Rugge et al. 2007) (Table 1) or OLGIM
13 (Capelle et al. 2010) (Table 2). As the diagnostic sensitivity increases with the number of
14 biopsies, it is advisable to take at least 2 biopsies in the antrum at the level of the large curva-
15 ture, one on the small curvature and 2 at the fundus (Jones et al. 2017; Fallone et al. 2016). To
16 properly assess atrophy, a biopsy should also be performed on the small curvature (Rugge et
17 al. 2007).

18 **3.2 Rapid urease test**

19 The rapid urease test is based on the activity of the urease produced by live *H. pylori*
20 (McNulty and Wise 1985). To perform the test, a gastric biopsy is placed in a medium contain-
21 ing urea and a colorimetric pH indicator. Following the ammonia production associated with

1 urease activity, the pH change is indicated by the colorimetric shift of the pH indicator. The
2 advantages of this test are its simplicity, its low cost and its ease of execution.

3 **3.3 Culture**

4 *H. pylori* culture is difficult because this bacterium is fragile and required microaerophilic
5 conditions to grow. However, its culture can be facilitated by the use of a transport medium in
6 the endoscopy room (Bontems et al. 2001; Koletzko et al. 2006; Miendje Deyi et al. 2011;
7 Jones et al. 2017). Culture has the advantage of being able to provide information on the sus-
8 ceptibility of strains to antibiotics, to adapt antimicrobial therapy and to improve the rate of
9 eradication (Miendje Deyi et al. 2011; Chan and Mackenzie 1986; Jones et al. 2017; Fallone
10 et al., 2016). Given the possible mixed infection with susceptible and resistant strains to a
11 given antimicrobial agents and the distribution of the bacteria in the stomach, it is recom-
12 mended to take several biopsies (at least one in the antrum and one in the fundus) (Selgrad et
13 al. 2014; Aguilera-Correa et al. 2017; Malfertheiner et al. 2017). If the transport time to the
14 laboratory exceeds 4 hours, biopsies should be kept frozen for a maximum of 24 hours.
15 Beyond this, it is best to freeze at -70°C or in liquid nitrogen (Miendje Deyi et al. 2011).

16 **3.4 Polymerase chain reaction (PCR)**

17 Molecular biology techniques can replace culture for the diagnosis of *H. pylori* infection if a
18 medical center does not have the technical capability and/or cannot send the frozen samples to
19 a microbiology department with that expertise. These techniques also allow the detection of
20 mutations causing resistance to certain antibiotics and the detection of infections with several
21 strains with different susceptibility profiles to antibiotics (Miendje Deyi et al. 2011; Kalach et
22 al. 2015).

1 **3.5 Serology**

2 Serology is a simple and very accessible method. A comparative study of 29 commercially
3 available serological kits to detect *H. pylori* infection came to the conclusion that some of the
4 available kits are excellent, with performance parameters such as sensitivity and specificity
5 above 90% (Burucoa et al. 2013). However, local validation of these tests is still needed as
6 their performance may vary depending on the antigenic composition of the circulating strains
7 in a given population. The persistence, sometimes prolonged of antibodies against *H. pylori*
8 does not allow to distinguish between an active and a cured infection. In addition, sensitivity
9 is low in young children although still frequently used in epidemiological studies (Westblom
10 et al. 1992; Andersen et al. 1994; Raymond et al. 1996; Corvaglia et al. 1999; Okuda et al.
11 2002; Douraghi et al. 2013). However, some recent publications suggest that newer serologi-
12 cal tests are more reliable in children (Shady et al. 2015; Kalach et al. 2017; Raj et al. 2017).
13 Enzyme-linked immunosorbent assay (ELISA)-based methods are always preferred over
14 rapid near-patient tests, whose performances are usually not satisfactory and with low
15 reproducibility (Best et al. 2018) .

16 **3.6 Urea breath test**

17 The marked urea breath test consists in having the patient swallow carbon-labeled urea, low-
18 radioactive ^{14}C or, particularly in children, the non-radioactive ^{13}C , and then assay this stable
19 isotope in the CO_2 expired. If the patient is infected, the labeled urea is metabolized by the
20 urease produced by *H. pylori* and the expired $^{13}\text{CO}_2$ increase is detected by a mass spectrome-
21 ter (Graham et al. 1987; Vandenplas et al. 1992; Cadranet et al. 1998). This test, undeniably
22 very sensitive, but expensive, has the advantage to detect the presence of the bacterium in the
23 entire stomach. However, children younger than 6 years appear to have a higher rate of false

1 positive urea breath test (Leal et al. 2011). The reported performance of the urea breath test
2 for detection of *H. pylori* infection in a recent study, in comparison with biopsy-based histo-
3 logic examination in 60 children, is low with a sensitivity of 76.2% and a specificity of 69.2%
4 in this age group (Honar et al. 2016). Many pitfalls were underlined to explain these poor re-
5 sults: patient compliance, consumption of PPIs and/or antibiotics for example. Therefore,
6 stool antigen tests with a monoclonal antibody are regarded as more convenient among young
7 people (Honar et al. 2016; Osaki et al. 2008). It is recommended for eradication control at
8 least 4 weeks after cessation of eradication treatment (Osaki et al. 2008; Malfertheiner et al.
9 2017; Jones et al. 2017).

10

11 **3.7 Stool Antigen test**

12 Antigen testing in stool is an alternative to the respiratory test for monitoring patients after
13 eradication treatment, epidemiology or test and treat strategies in selected populations, with
14 the proviso that only monoclonal antibody tests with good sensitivity should be used
15 (Makristathis et al. 1998). *H. pylori* specific antigen is tested in fresh or frozen stool samples
16 (Guarner et al. 2010).

17 **4. Risk factors of *H. pylori* infection**

18 It is now well established that *H. pylori* infection is mostly acquired during childhood, mainly
19 during the first 5 years of life and it is significantly influenced by geographical context and
20 specific living conditions (Mendall et al. 1992). In developing countries, the prevalence of the
21 infection is 30 to 50% in children and reaches 90% in adults. In contrast, in developed coun-
22 tries the prevalence of the infection in children is between 1 to 12% and reaches 30 to 50% in

1 adults (Suerbaum and Michetti 2002). These differences among underdeveloped and indus-
2 trialized countries are mainly due to the impact of risk factors during childhood. According to
3 a large number of studies, the main routes of *H. pylori* transmission are person to person by
4 oral-oral or fecal-oral routes. The level of contamination is strongly dependent of familial and
5 environmental parameters, with a more drastic impact of living environment including poor
6 hygiene and sanitation which are promoting factors for *H. pylori*, especially in developing
7 countries. However, either for developing or developed countries, familial socioeconomic sta-
8 tus is the main risk factor for *H. pylori* infection among children.

10 **4.1 Socioeconomic status and environmental conditions**

11 *4.1.a Familial context and source of transmission*

12 The socioeconomic status is defined as occupation, family income level, parent's education
13 level, and living conditions including crowding occupancy. Abundant evidences from many
14 studies demonstrated that low socioeconomic status is a major risk factor in the acquisition of
15 *H. pylori* infection (Fig. 2). This is particularly true as while a declining trend in overall pre-
16 valence over time of *H. pylori* infection among industrialized countries, poor socioeconomic
17 conditions still remain associated with a high prevalence. There is no difference in this respect
18 between the developed and the developing countries. For example, in the United States, the
19 prevalence of *H. pylori* infection was approximately twice as high among black and hispanic
20 populations compared to age-matches whites (Malaty et al. 1992). More recently, the preva-
21 lence of *H. pylori* infection has been determined in a cohort of Portuguese adolescents
22 (EpiTeen) at the age of 13 and the incidence after a 3 years follow-up was analyzed. An in-
23 verse association was found between the prevalence of the infection and the parent's educa-

1 tion level. The adolescents studying in private school were less likely to be infected (Bastos et
2 al. 2013). A recent nationally representative cross-sectional study involving adults ≥ 18 years
3 old in Turkey, where the overall prevalence of *H. pylori* infection is about 82.5%, also con-
4 firmed an inverse association of education level and *H. pylori* infection. In addition, indivi-
5 duals who had access to social security were at lower risk of *H. pylori* infection (Ozaydin et
6 al. 2013). While education was the only significant factor for women, residential region, hou-
7 sing tenure were among risk factors for men.

8 Although the link between several risk factors and a high prevalence of *H. pylori* infection
9 is well established, the way of its transmission is still unclear. However, interpersonal and in-
10 trafamilial transmissions either oral-oral or fecal-oral appear to be the main route, as sup-
11 ported by a recent study which confirmed that bed sharing, and two affected parents were po-
12 sitively associated with the presence of *H. pylori* infection (Hasosah et al. 2015). Already in
13 the 90's, confined-living conditions as crowded sleeping accommodation was strongly asso-
14 ciated with the presence of infection among children (Mendall et al. 1992). In line with this,
15 Bastos et al. (2013) showed that more siblings and living in a house with higher crowding in-
16 dex were also positive risk factors. In urban and rural Beninese populations, 406 healthy indi-
17 viduals including 240 and 206 subjects, respectively, were selected from 96 households. The
18 risk of *H. pylori* infection in children was 13-fold higher when both parents were *H. pylori*
19 positive (95% OR=13.6, 95% Confidence Interval 3.63-51.22), compared with when only one
20 parent was positive (95% OR=5.3, 95% Confidence Interval 1.52-18.45) (Aguemon et al.
21 2005). In this study, while the spread of infection is facilitated by living conditions with high
22 promiscuity and a high transmission from infected parents to children, a high number of si-
23 blings has been reported as another risk factor. A multilocus sequence typing (MLST) DNA
24 analysis using the stools of parents belonging to three families showed an intrafamilial trans-

1 mission in all selected families with a mother-to-child transmission in at least two families
2 (Osaki et al. 2013). In addition, a grand-mother to child transmission has also been suggested
3 by Urita et al. (2013), who tested 838 children from a small town in Japan. Furthermore, a
4 transmission from sibling to sibling has also been proposed by a macroarray study on selected
5 *H. pylori* coding sequences (CDS) on three families including one child with persistence of
6 gastric symptoms after antibiotics treatment (Raymond et al. 2008). The analysis on 684 chil-
7 dren from rural Andean area screened for *H. pylori* with the ¹³C-urea breath test indicates that
8 the infection is mostly transmitted among siblings which are close in age, and most frequently
9 from the older to younger ones (Goodman and Correa 2000). This was also confirmed in po-
10 pulation with low overall prevalence of *H. pylori* as reported by Sykora et al. (2009) who
11 developed a cross-sectional population-based study on 1,545 asymptomatic Czech children
12 (aged 0-15 years) where the prevalence was 7.1%. A positive association with *H. pylori* infec-
13 tion was found with the number of children in a household and the lack of formal education of
14 fathers. Also related to the social status of the family, the access to good hygiene living condi-
15 tion limits the prevalence of the infection, indicating that important risks factors are asso-
16 ciated to poverty. There is no difference in this respect between the developed and the deve-
17 loping countries. In addition to intrafamilial transmission, spread of *H. pylori* infection can be
18 promoted by community living conditions. Indeed, the institutionalization of children between
19 1 and 6 years old was significantly associated with *H. pylori* infection as reported in asymp-
20 tomatic Czech children (Sykora et al. 2009). Among children living in urban area, a higher
21 risk of *H. pylori* seropositivity was significantly found associated for those who attended day
22 care centers or nurseries (Dore et al. 2002).

23

24 *4.1.a-1 Breast-feeding*

1 Whether or not children were breast-fed did not have a statistically significant effect on *H.*
2 *pylori* seropositivity among children living in adjacent urban and rural areas as reported by
3 Dore et al. (2002) in Northern Sardinia, Italy. However, the prospective population-based stu-
4 dy from the Czech Republic among asymptomatic children reported a higher prevalence of *H.*
5 *pylori* infection among children who had never been breast-fed (Sykora et al., 2009). In con-
6 trast, no correlation among children from low socioeconomic backgrounds in Lagos, Nigeria
7 was observed either with exclusive breast-feeding or its duration, and *H. pylori* infection
8 (Senbanjo et al. 2014). According to the history of breast-feeding (ever vs. never), a recent
9 systematic review (Carreira et al. 2015), did not find a significant association between breast-
10 feeding and *H. pylori* infection in either high- or middle-income countries, excepted children
11 having been breast-fed for 4-6 months which showed a lower risk of *H. pylori* infection only
12 in the middle-outcome countries. It was then proposed that breast-feeding may protect chil-
13 dren against infection by acting as natural antibiotics. Accordingly, children whose mothers
14 had breast milk with higher levels of anti-*H. pylori* IgA had a lower risk to be infected com-
15 pared with those whose mothers had lower levels (Thomas et al. 1993).

16

17 4.1.a-2 Microbiota

18 Gut microbiota composition can be affected by many factors among which diet, environ-
19 mental compounds, lifestyle habits, infection and disease (Rodriguez et al. 2015). A recent
20 study reported different profile of gastric microbiota composition when comparing between
21 gastric cancer and chronic gastritis patients (Ferreira et al. 2018). In this study, the gastric car-
22 cinoma dysbiosis is characterized by reduced microbial diversity with a reduced *Helicobacter*
23 abundance. A reduced microbial diversity is recognised as associated with disease states, as

1 also reported for inflammatory diseases and cancer (Gevers et al. 2014 ; Ahn et al. 2013). The
2 presence of *H. pylori* not only influence the composition of gastric microbiota but also indi-
3 rectly it modifies the intestinal microbiota, as demonstrated by Kienesberger et al (2016) in
4 the mouse model. As also reported by Arnold et al. (2011) the presence of *H. pylori* infection
5 induces a differential immune response, based on mouse age, that could affect the susceptibi-
6 lity of its host to disease and infection. Family microbiota is shared between parents and chil-
7 dren and may play an important role in the composition of infant microbiota. Whether intesti-
8 nal microbiota can affect *H. pylori* intrafamilial infection has been investigated (Osaki et al.
9 2018). The microbiota composition of 18 fecal specimens from five *H. pylori*-infected chil-
10 dren and their family members were analysed in five families. The microbiota from *H. pylori*-
11 positive children and adults showed a lower diversity than that of *H. pylori*-negative children
12 and parents. This study indicates that the similarity in microbiota composition and its poor di-
13 versity can be a risk factor for *H. pylori* intrafamilial transmission.

14

15 *4.1.b Environmental context*

16 The environment may serve as a reservoir for *H. pylori* infection and directly associated
17 risk factors may play an important role, even more important than familial socioeconomic sta-
18 tus especially in developing countries.

19

20 *4.1.b-1 Rural vs. urban living conditions*

21 The difference between urban and rural living conditions is also among factors influencing
22 the prevalence of *H. pylori* acquisition in children, in different countries. A cross-sectional
23 study conducted among Italian children residing in different environments (urban vs. rural) in

1 the north of Sardinia showed a prevalence of *H. pylori* infection of 26% among children aged
2 14-16 compared to 20% for those of 5-7 years-old. The prevalence was higher among chil-
3 dren living in rural area (36%) compared to among children residing in the urban area (13%).
4 This difference was age-independent (Dore et al. 2002). Especially in the rural areas, contact
5 with dogs is a promoting factor. While no association was seen between the prevalence of the
6 infection and the occupation of the head of the house in rural area, the seroprevalence of *H.*
7 *pylori* was directly associated with the socioeconomic status of parents in urban area. The
8 same data are also reported on population with different living conditions compared to Euro-
9 pean countries, as in a study on dyspeptic patients in Andkhoy (Afghanistan) where the posi-
10 tive prevalence for *H. pylori* has been associated with epigastric pain and rural occupancy
11 with a positive correlation with illiteracy (Hamrah et al. 2017). In contrast, in the Beninese
12 population, no significant differences were observed on the prevalence of the infection bet-
13 ween rural and urban areas (Aguemon et al. 2005).

14 4.1.b-2 Water and access to sanitary and hygiene

15 According to many epidemiologic studies, water could be an important source of *H. py-*
16 *lori* contamination (Ozaydin et al. 2013). Particularly in developing countries waterborne in-
17 fection is the main infection route of *H. pylori* due to poor sanitary distribution of water
18 among the population. As example in Peru, the analysis of drinking water samples from diffe-
19 rent locations, based on PCR assays on specific *H. pylori* genes, showed that the majority of
20 contaminated water came from municipal water (Hulten et al. 1996). In contrast, only three of
21 25 municipal water samples analyzed in Sweden showed the presence of *Helicobacter spp.*
22 DNA, while a large number of well water samples were positive in PCR assays (Hulten et al.
23 1996). *H. pylori* DNA was also detected in well water in Japan, whose consumers were de-
24 tected positive for *H. pylori* infection (Horiuchi et al. 2001). Accordingly, a study conducted

1 in Germany indicated a positive association for *H. pylori* infection and consumption of well
2 water (Strebel et al. 2010), as also reported in Portugal (Amaral et al. 2017). In addition, a ri-
3 ver water-associated *H. pylori* contamination has also been suggested in Japan (Fujimura et
4 al. 2008).

5 The potential presence of live *H. pylori* infective cells in water samples is of public health
6 concern. The analysis of 45 wastewater samples obtained from two secondary wastewater
7 treatment plants in Valencia, Spain showed the presence of culturable *H. pylori* isolates
8 (Moreno and Ferrus 2012). These findings support that fecal-contaminated water may act as a
9 reservoir for *H. pylori* spread. It has been suggested that the ability of *H. pylori* to form bio-
10 film may allow its survival in natural water sources and water distribution systems (Garcia et
11 al. 2014). In addition to DNA detection, about less than 10 reports indicate that culturable
12 form of *H. pylori* can be isolated from water samples as reviewed by Aziz et al. 2015. *H. py-
13 lori* cultivability in water should be limited in time with an optimum <10h at temperatures
14 over 20°C (Adams et al. 2003 ; Azevedo et al. 2008). The acquisition of culturable phenotype
15 in water is associated to morphological transition of the bacterium to the rod shape implica-
16 ting the peptidoglycane (PG) turnover (Fernandes et al. 2017). Accordingly, *H. pylori* enters a
17 viable but not culturable (VBNC) state within a few days after inoculation into water, asso-
18 ciated to morphological changes from a spiral bacillus to coccoid form. While the exposition
19 of mice to *H. pylori* viable strain SS1-supplemented drinking water led to infection in mice
20 with significant gastric inflammation after 4 weeks (Boehnke et al. 2015), waterborne VBNC
21 SS1 failed to colonize mice either through drinking water exposure or oral gavage (Boehnke
22 et al. 2017).

23

24 4.2 Lifestyle habits

1 4.2.a Food

2 Several studies detected the presence of *H. pylori* DNA in dairy products and especially raw
3 milk (Momtaz et al. 2014), that has been considered as the main source of food transmission.
4 About 19% of raw milk and dairy product samples tested in Iran were found *H. pylori*-
5 positive (Mousavi et al. 2014). Ovine milk and traditional cheese were the most commonly
6 contaminated products as reported by Dore et al. (1999b) which detected the presence of *H.*
7 *pylori* by PCR amplification in milk samples from sheeps, thus indicating a potential conta-
8 mination of humans by milk consumption. Similar data were also reported for raw cow milk
9 samples in Japan (Fujimura et al. 2002), as well as in Greeks (Angelidis et al. 2011) and Ame-
10 rican (Dore et al. 2001) herds. Supporting these data, a recent study reports a higher preva-
11 lence of *H. pylori* positively associated with the consumption of milk (Assaad et al. 2018).
12 The contamination of milk may be also related to lack of hygiene measure during milk pro-
13 cessing and especially from unpasteurized milk storage in some countries. An important fin-
14 ding from Mousavi et al. (2014) was the high presence of *H. pylori* antibiotic resistant strains
15 isolated from milk and dairy products.

16 Meat has also been proposed as a possible source of *H. pylori* reservoir. Previous data
17 identified the presence of *H. pylori* by 16SrRNA and *vacA* PCR analysis in gastric tissues
18 from sheep, thus taking part in the human food chain. Sheeps have been proposed as a source
19 of *H. pylori* transmission among shepherds and their family members (Dore et al., 1999a)
20 (Papiez et al. 2003). In line with this, the prevalence of *H. pylori* infection among shepherds,
21 who reside in Northern Sardinia and among members of their family is one of the highest in
22 the world (98%). It may be associated with direct contact with sheeps and sheepdogs (Dore et

1 al. 1999a) (Dore et al. 1999b), as also reported in Colombian Andes population (Goodman et
2 al. 1996).

3 Raw vegetables may be also a source of *H. pylori* food transmission to humans. Several
4 studies reported the detection of *H. pylori* by culture and PCR in vegetable and salad samples
5 (Goodman et al. 1996; Yahaghi et al. 2014). Contaminated water used through washing may
6 be likely the source of the presence of *H. pylori* in raw vegetables. Thus, the lack or deficient
7 waste water treatment may also promote *H. pylori* food contamination and it is likely to play
8 an important role in *H. pylori* transmission to humans. However, given the link between *H.*
9 *pylori* infection and low socioeconomic status, the infection could occur predominantly
10 among individuals with deficient nutritional status. In the Andean population in Columbia, *H.*
11 *pylori* infection occurred more frequently among children of short stature for their age, with a
12 low consumption of fruits and vegetables associated with low nutritional indicators
13 (Goodman et al. 1997).

14 4.2.b. Alcohol drinking and smoking habits

15 Studies on the association of smoking and alcohol consumption with *H. pylori* infection
16 showed conflicting results. While Zhu et al. (2014) reported that the use of alcohol and tobac-
17 co had no impact on the prevalence of *H. pylori* infection, significant relationships between
18 smoking habits (current vs. never) with *H. pylori* seropositivity have been reported in Ja-
19 panese adults (Kikuchi et al. 1998). In Northern Ireland, smoking has been reported positively
20 associated with the presence of *H. pylori* infection, however, no relationship with alcohol
21 consumption has been found to be significant (Murray et al. 1997). In contrast, the study by
22 Ogihara et al. (2000) which analyzed the impact of drinking and smoking on *H. pylori* serolo-
23 gy in 8837 subjects working in textile companies in Japan, found a negative association bet-

1 ween current cigarette and alcohol consumption with *H. pylori* seropositivity. The increased
2 gastric acidity associated to smoking may be a cause of the negative association between the
3 presence of the infection and tobacco consumption. Furthermore, more recently non-smokers
4 and regular alcohol consumers were suggested as under less risk of *H. pylori* infection than
5 others (Ozaydin et al. 2013).

6

7 **4.3 Occupational hazards**

8 The occupational risk for acquiring *H. pylori* infection has been addressed in several stu-
9 dies among healthcare workers during contact with patients. The prevalence of *H. pylori* in-
10 fection has been evaluated by immunoassay on stool samples from 249 subjects employed in
11 a university teaching hospital according to three categories of hospital workers including per-
12 sonal from gastrointestinal endoscopy unit, personal and staff from other hospital units either
13 with direct or no contact with patients. The results indicated that hospital work involving di-
14 rect contact with patients constitutes a major risk factor for *H. pylori* contamination compared
15 with hospital work without direct contact with patients (Mastromarino et al. 2005). Accor-
16 dingly, nursing staff was also demonstrated as higher risk of *H. pylori* infection compared to
17 administrative and technical staff (Triantafillidis et al. 2002). In addition, during the 5 years
18 of following, a higher seroconversion for subjects initially *H. pylori* negative which became
19 positive, was observed for the nursing staff category. It is interesting to notice, that also in
20 that study, the level of education was inversely associated with the prevalence of the infec-
21 tion.

1 **5 Conclusions**

2 Even though recent research suggests that the prevalence of *H. pylori* infection trends
3 to decrease in most of the countries, it remains high in most of developing countries as also il-
4 lustrated with immigrant populations coming from countries with a high prevalence. The
5 main risk factors remain associated with socioeconomic, familial living conditions and envi-
6 ronmental factors. These data highlight the importance of the identification of population-
7 specific risk factors as *H. pylori* reservoir that will allow to develop efficient preventive stra-
8 tegies to limit the prevalence of *H. pylori* infection among the most vulnerable populations.

9

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Atrophy score		Corpus			
		No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (including incisura angularis)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1) (including incisura angularis)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2) (including incisura angularis)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3) (including incisura angularis)	Stage III	Stage III	Stage IV	Stage IV

1

2 **Table 1: Gastritis staging according to OLGA classification.**

3 The Operative Link on Gastritis Assessment (OLGA) system corresponds to an histological
4 staging for gastric inflammation, considering gastric atrophy as the histological lesion repre-
5 sentative of disease progression. From Rugge et al. (2007) with permission.

6

IM score		Corpus			
		Not fat: no IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
Antrum (including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

7

8 **Table 2: Gastritis staging according to OLGIM classification**

9 The Operative Link on Gastric Intestinal Metaplasia (OLGIM) system corresponds to an his-
10 tological staging for gastric inflammation, considering intestinal metaplasia (IM) as the
11 histological lesion representative of disease progression. From Capelle et al. (2010) with
12 permission.

1 **Legends of figures**

2

3 **Figure 1: The updated Sydney classification for gastric lesions.**

4 Each feature is assigned with a semi-quantitative and descriptive evaluation to 0: absence
5 (Normal), 1 for mild, 2 for moderate and 3 for marked corresponding modification including
6 infiltration of neutrophils and mononuclear cells, intensity of atrophy and frequency and severity of intestinal metaplasia. Taken from Dixon et al. (1996) with permission.

8

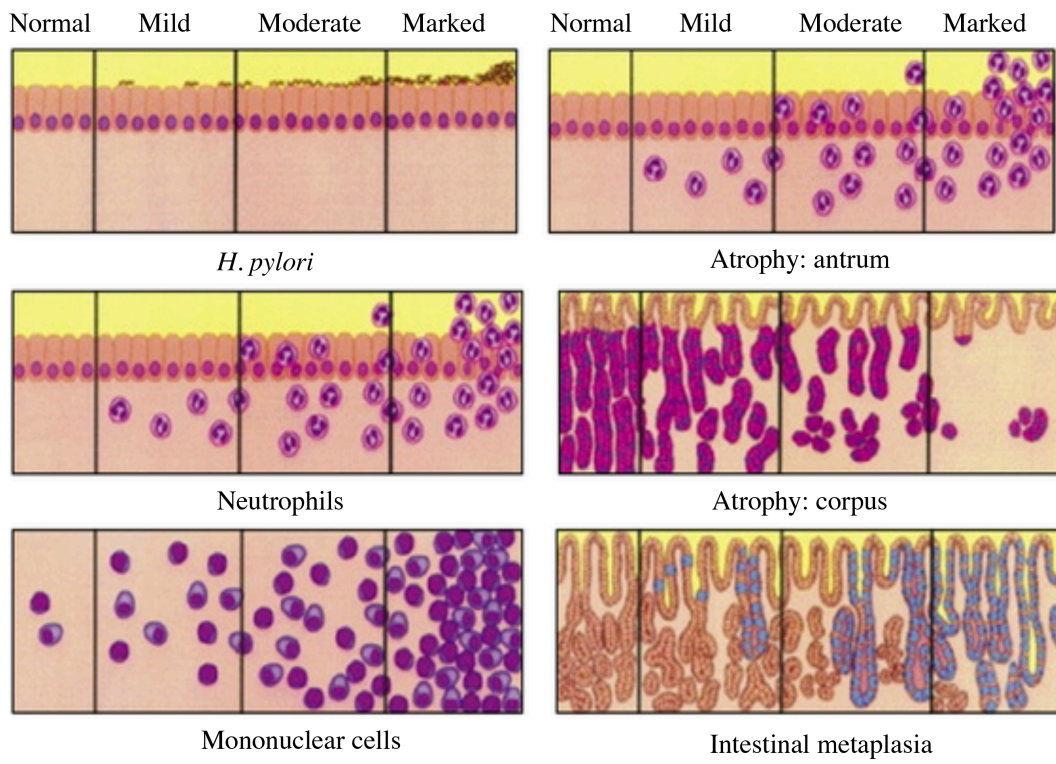
9 **Figure 2 : Risk factors associated to *H. pylori* infection.**

10 Major risk factors associated to the transmission and spread of *H. pylori* are of multiple ori-
11 gins including familial and living conditions, life style habits and environmental context. Mi-
12 crobiota and breast-feeding correspond to individual factors suggested to modulate the trans-
13 mission/acquisition of *H. pylori* infection.

14

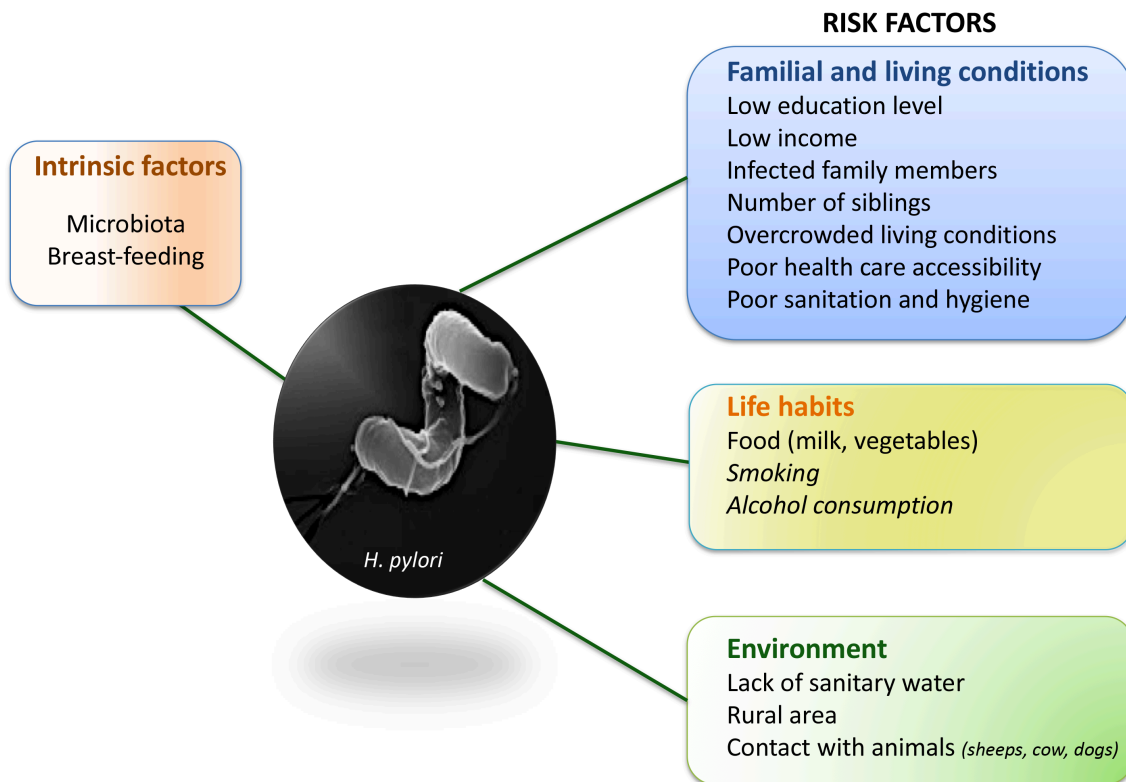
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16



1

2 **Fig.1**



1

2 **Fig. 2**