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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.

9

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

1 **References**

- 2 Abdul Rahim NR, Benson J, Grocke K, Vather D, Zimmerman J, Moody T, Mwanri L (2017)
3 Prevalence of *Helicobacter pylori* infection in newly arrived refugees attending the
4 Migrant Health Service, South Australia. *Helicobacter* 22 (2).
5 <https://doi.org/10.1111/hel.12360>
- 6 Adams BL, Bates TC, Oliver JD (2003) *Helicobacter pylori* in a natural freshwater environ-
7 ment. *Appl Environ Microb* 69(12) :7462-7466. [10.1128/AEM.69.12.7462-7466.2003](https://doi.org/10.1128/AEM.69.12.7462-7466.2003)
- 8 Aguemou BD, Struelens MJ, Massougbdji, Ouendo EM (2005) Prevalence and risk-factors
9 for *Helicobacter pylori* infection in urban and rural Beninese populations. *Clin Microbiol*
10 *Infect* 11(8) 611-617. <https://doi.org/10.1111/j.1469-0691.2005.01189.x>
- 11 Aguilera-Correa JJ, Urruzuno P, Barrio J, Martinez MJ, Agudo S, Somodevilla A, Liorca L,
12 Alarcon T (2017) Detection of *Helicobacter pylori* and the genotypes of resistance to
13 clarithromycin and the heterogeneous genotype to this antibiotic in biopsies obtained
14 from symptomatic children. *Diag Microbiol Infect Dis* 87(2):150-153.
15 <https://doi.org/10.1016/j.diagmicrobio.2016.03.001>
- 16 Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, Goedert IJ, Hayes RB, Yang L (2013)
17 Human gut microbiome and risk for colorectal cancer. *J Natl Cancer Inst* 105(24) :1907-
18 1911. <https://doi.org/10.1093/jnci/djt300>
- 19 Amaral O, Fernandes I, Veiga N, Pereira C, Chaves C, Nelas P, Silva D (2017) Living
20 Conditions and *Helicobacter pylori* in Adults. *Biomed Res Int* 2017:9082716.
21 <https://doi.org/10.1155/2017/9082716>
- 22 Andersen LP, Wewer AV, Christiansen KM, Tvede M, Hansen JP, Henriksen FW,
23 Krasilnikoff PA (1994) The humoral immune response to *Helicobacter pylori* infection in
24 children with recurrent abdominal pain. *APMIS* 102(6):457-464.
- 25 Angelidis AS, Tirodimos I, Bobos M, Kalamaki MS, Papageorgiou DK, Arvanitidou M
26 (2011) Detection of *Helicobacter pylori* in raw bovine milk by fluorescence in situ
27 hybridization (FISH). *Int J Food Microbiol* 151(2):252-256.
28 <https://doi.org/10.1016/j.ijfoodmicro.2011.09.007>
- 29 Arnold IC, Dehzad N, Reuter S, Martin H, Becher B, Taube C, Müller A (2011) *Helicobacter*
30 *pylori* infection prevents allergic asthma in mouse models through the induction of regu-
31 latory T cells. *J Clin Invest* 121 :3088-3093. <https://doi.org/10.1172/JCI45041>
- 32 Asgeirsdottir GA, Kjartansdottir I, Olafsdottir AS, Hreinsson JP, Hrafnkelsson H, Johannsson
33 E, Björnsson ES (2017) *Helicobacter pylori* infection in Icelandic children. *Scand J*
34 *Gastroenterol* 52(6-7):686-690. <https://doi.org/10.1080/00365521.2017.1304986>
- 35 Assaad S, Chaaban R, Tannous F, Costanian C (2018) Dietary habits and *Helicobacter pylori*
36 infection: a cross sectional study at a Lebanese hospital. *BMC Gastroenterology*
37 18(1):48. <https://doi.org/10.1186/s12876-018-0775-1>
- 38 Azevedo NF, Almeida C, Fernandes I, Cerqueira L, Dias S, Keevil CW, Vieira JM (2008)
39 Survival of gastric and enterohepatic helicobacter spp. In water. Implications for trans-
40 mission. *Appl Environ Microbiol* 74(6):1805-1811. [10.1128/AEM.02241-07](https://doi.org/10.1128/AEM.02241-07)
- 41 Aziz RK, Khalifa MM, Sharaf RR (2015) Contaminated water as a source of *Helicobacter py-*
42 *lori* infection : a review. *J Adv Res* 6 : 539-547.
43 <http://dx.doi.org/10.1016/j.jare.2013.07.007>
- 44 Bastos J, Peleteiro B, Pinto H, Marinho A, Guimaraes JT, Ramos E, La Vecchia C, Barros H,
45 Lunet N (2013) Prevalence, incidence and risk factors for *Helicobacter pylori* infection in

- 1 a cohort of Portuguese adolescents (EpiTeen). *Dig Liver Dis* 45(4):290-295.
2 <https://doi.org/10.1016/j.dld.2012.11.009>
- 3 Best LM, Takwoingi Y, Siddique S, Selladurai A, Gandhi A, Low B, Yaghoobi M, Gurusamy
4 KS (2018) Non-invasive diagnostic tests for *Helicobacter pylori* infection. *Cochren*
5 *Database Syst Rev* 3:CD012080. <https://doi.org/10.1002/14651858.CD012080.pub2>
- 6 Biernat MM, Iwanczak B, Binkowska A, Grabinska J, Gosciniak G (2016) The prevalence of
7 *Helicobacter pylori* infection in symptomatic children: a 13-year observational study in
8 the lower Silesian region. *Adv Clin Exp Med* 25(2):303-308.
9 <https://doi.org/10.17219/acem/44372>
- 10 Boehnke KF, Eaton KA, Fontaine C, Brewster R, Wu J, Eisenberg JNS, Valdivieso M, Baker
11 LH, Xi C (2017) Reduced infectivity of waterborne viable but nonculturable
12 *Helicobacter pylori* strain SS1 in mice. *Helicobacter*, 22(4).
13 <https://doi.org/10.1111/hel.12391>
- 14 Boehnke KF, Eaton KA, Valdivieso M, Baker LH, Xi C (2015) Animal model reveals
15 potential waterborne transmission of *Helicobacter pylori* infection. *Helicobacter*,
16 20(5):326-333. <https://doi.org/10.1111/hel.12216>
- 17 Bontems P, Devaster JM, Corvaglia L, Dezsöfi A, Van Den Borre C, Goutier S, Butzler JP,
18 Cadranel S (2001) Twelve year observation of primary and secondary antibiotic-resistant
19 *Helicobacter pylori* strains in children. *Pediatr Infect Dis J* 20(11):1033-1038.
- 20 Burucoa C, Delchier JC, Courillon-Mallet A, de Korwin JD, Mégraud F, Zerbib F, Raymond
21 J, Fauchère JL (2013) Comparative evaluation of 29 commercial *Helicobacter pylori*
22 serological kits. *Helicobacter* 18(3):169-179. <https://doi.org/10.1111/hel.12030>
- 23 Cadranel S, Corvaglia L, Bontems P, Deprez C, Glupczynski Y, Van Riet A, Keppens E
24 (1998) Detection of *Helicobacter pylori* infection in children with a standardized and
25 simplified ¹³C-urea breath test. *J Pediatr Gastroenterol Nutr* 27(3):275-280.
- 26 Capelle LG, De Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, van Dekken H,
27 Meijer J, van Grieken NC, Kuipers EJ (2010) The staging of gastritis with the OLGA
28 system by using intestinal metaplasia as an accurate alternative for atrophic gastritis.
29 *Gastrointest Endosc* 71(7):1150-1158. <https://doi.org/10.1016/j.gie.2009.12.029>
- 30 Cardenas VM, Mulla ZD, Ortiz M, Graham DY (2006) Iron deficiency and *Helicobacter*
31 *pylori* infection in the United States. *Am J Epidemiol* 163(2): 127-134.
32 <https://doi.org/10.1093/aje/kwj018>
- 33 Carreira H, Bastos A, Peleteiro B, Lunet N (2015) Breast-feeding and *Helicobacter pylori*
34 infection: systematic review and meta-analysis. *Public Health Nutr* 18(3):500-520.
35 <https://doi.org/10.1017/S1368980014000500>
- 36 Chan FT, Mackenzie AM (1986) Evaluation of primary selective media and enrichment
37 methods for *Campylobacter* species isolation. *Eur J Clin Microbiol* 5(2):162-164.
- 38 Correa P (1992) Human gastric carcinogenesis: a multistep and multifactorial process. First
39 American Cancer Society Award Lecture on Cancer Epidemiology and Prevention.
40 *Cancer Res* 52(24):6735-6740.
- 41 Correa P, Piazuelo MB (2011) *Helicobacter pylori* infection and gastric adenocarcinoma. *US*
42 *Gastroenterol Hepatol Rev* 7(1):59-64.
- 43 Corvaglia L, Bontems P, Devaster JM, Heimann P, Glupczynski Y, Keppens E, Cadranel S
44 (1999) Accuracy of serology and ¹³C-urea breath test for detection of *Helicobacter pylori*
45 in children. *Pediatr Infect Dis J* 18(11):976-979.
- 46 Daugule I, Karklina D, Rudzite D, Remberga S, Rumba-Rozenfelde I (2016) Prevalence of
47 *Helicobacter pylori* infection among preschool children in Latvia: no significant decrease

- 1 in prevalence during a ten year period. Scand J Public Health 44(4):418-422.
2 <https://doi.org/10.1177/1403494816631861>
- 3 Dixon MF, Genta RM, Yardley JH, Correa P (1996) Classification and grading of gastritis.
4 The updated Sydney System. International Workshop on the Histopathology of Gastritis,
5 Houston 1994. Am J Surg Pathol 20(10):1161-1181.
- 6 Dore MP, Bilotta M, Vaira D, Manca A, Massarelli G, Leandro G, Atzei A, Pisanu G,
7 Graham DY, Realdi G (1999a) High prevalence of *Helicobacter pylori* infection in
8 shepherds. Dig Dis Sci 44(6):1161-1164.
- 9 Dore MP, Sepulveda AR, Osato MS, Realdi G, Graham DY (1999b) *Helicobacter pylori* in
10 sheep milk. Lancet 354(9173):132. [https://doi.org/10.1016/S0140-6736\(99\)01724-9](https://doi.org/10.1016/S0140-6736(99)01724-9)
- 11 Dore MP, Malaty HM, Graham DY, Fanciulli G, Delitalia G, Realdi G (2002) Risk Factors
12 Associated with *Helicobacter pylori* infection among children in a defined geographic
13 area. Clin Infect Dis 35(3):240-245. <https://doi.org/10.1086/341415>
- 14 Dore MP, Sepulveda AR, Al-Zimaity H, Yamaoka Y, Osato MS, Mototsugu K, Nieddu AM,
15 Realdi G, Graham DY (2001) Isolation of *Helicobacter pylori* from sheep-implications
16 for transmission to humans. Am J Gastroenterol 96(5):1396-1401.
17 <https://doi.org/10.1111/j.1572-0241.2001.03772.x>
- 18 Douraghi M, Nateghi Rostami M, Goudarzi H, Ghalavand Z (2013) Comparison of stool
19 antigen immunoassay and serology for screening for *Helicobacter pylori* infection in
20 intellectually disabled children. Microbiol Immunol 57(11):772-777.
21 <https://doi.org/10.1111/1348-0421.12099>
- 22 Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ (1999) Association of *Helicobacter pylori*
23 infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol 94(9): 2373-2379.
24 <https://doi.org/10.1111/j.1572-0241.1999.01360.x>
- 25 Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G (2000)
26 Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in
27 the United States. J Infect Dis 181:1359-1363. <https://doi.org/10.1086/315384>
- 28 Fallone CA, Chiba N, Van Zanten S, Fischbach L, Gisbert JP, Hunt RH, Jones NL, Render C,
29 Leontiadis GI, Moayyedi P, Marshall JK (2016) The Toronto consensus for the treatment
30 of *Helicobacter pylori* Infection in Adults. Gastroenterology, 151(1):51-69.
31 <https://doi.org/10.1053/j.gastro.2016.04.006>
- 32 Fernandes RM, Silva H, Oliveira R, Almeida C, Azevedo NF, Vieira MJ (2017) Morphologi-
33 cal transition of *Helicobacter pylori* adapted to water. Future Microbiol 12(13):1167-
34 1179. <https://doi.org/10.2217/fmb-2016-0174>
- 35 Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC,
36 Figueiredo C (2018) Gastric microbial community profiling reveals a dysbiotic cancer as-
37 sociated microbiota. Gut 67(2):226-236. <http://dx.doi.org/10.1136/gutjnl-2017-314205>
- 38 Fujimura S, Kato S, Watanabe A (2008) Water source as a *Helicobacter pylori* transmission
39 route: a 3-year follow-up study of Japanese children living in a unique district. J Med
40 Microbiol 57(Pt 7):909-910. <https://doi.org/10.1099/jmm.0.47683-0>
- 41 Fujimura S, Kawamura T, Kato S, Tateno H, Watanabe A (2002) Detection of *Helicobacter*
42 *pylori* in cow's milk. Lett Appl Microbiol 35(6):504-507.
43 <https://doi.org/10.1046/j.1472-765X.2002.01229.x>
- 44 Garcia A, Salas-Jara MJ, Herrera C, Gonzalez C (2014) Biofilm and *Helicobacter pylori*:
45 from environment to human host. World J Gastroenterol 20(19):5632-5638.
46 <https://doi.org/10.3748/wjg.v20.i19.5632>
- 47 Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Van Treuren W, Ren B, Schwager
48 E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, Gonzalez A, McDo-

- 1 nald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J,
2 Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Hut-
3 tenhower C, Knight R, Xavier RJ (2014) The treatment-naive microbiome in new onset
4 Crohn's disease. *Cell Host Microbe* 15(3):382-392. doi:10.1016/j.chom.2014.02.005.
- 5 Goodman KJ, Correa P (2000) Transmission of *Helicobacter pylori* among siblings. *Lancet*,
6 355(9201):358-362. [https://doi.org/10.1016/S0140-6736\(99\)05273-3](https://doi.org/10.1016/S0140-6736(99)05273-3)
- 7 Goodman KJ, Correa P, Tengana Aux HJ, DeLany JP, Collazos T (1997) Nutritional factors
8 and *Helicobacter pylori* infection in Colombian children. *J Pediatr Gastroenterol Nutr*
9 25(5):507-515.
- 10 Goodman KJ, Correa P, Tengana Aux HJ, Ramirez H, DeLany JP, Guerrero Pepinosa O,
11 Lopez Quinones M, Collazos Parra T (1996) *Helicobacter pylori* infection in the
12 Colombian Andes: a population-based study of transmission pathways. *Am J Epidemiol*
13 144(3):290-299.
- 14 Graham DY, Klein PD, Evans DJ Jr, Evans DG, Alpert LC, Opekun AR, Boutton TW (1987)
15 *Campylobacter pylori* detected noninvasively by the 13C-urea breath test. *Lancet*
16 1(8543):1174-1177. [https://doi.org/10.1016/S0140-6736\(87\)92145-3](https://doi.org/10.1016/S0140-6736(87)92145-3)
- 17 Graham DY, Lu H, Yamaoka Y (2009) African, Asian or Indian enigma, the East Asian
18 *Helicobacter pylori*: facts or medical myths. *J Dig Dis* 10(2):77-84.
19 <https://doi.org/10.1111/j.1751-2980.2009.00368.x>
- 20 Guarner J, Kalach N, Elitsur Y, Koletzko S (2010) *Helicobacter pylori* diagnostic tests in
21 children: review of the literature from 1999 to 2009. *Eur J Pediatr* 169(1):15-25.
22 <https://doi.org/10.1007/s00431-009-1033-x>
- 23 Hamrah MH, Hamrah MS, Hassan Hamrah M, Kanda M, Hamrah AE, Dahi AE, Homayoun
24 F, Hamrah MH, Fotouhi A, Sakamoto J (2017) Prevalence of *Helicobacter pylori*
25 infection in dyspeptic patients in Andkhoy Afghanistan. *Asian Pac J Cancer Prev*
26 18(11):3123-3127. <https://doi.org/10.22034/APJCP.2017.18.11.3123>
- 27 Hasosah M, Satti M, Shehzad A, Alsaifi A, Sukkar G, Alzaben A, Sunaid A, Ahmed A,
28 AlThubiti S, Mufti A, Jacobson K (2015) Prevalence and risk factors of *Helicobacter*
29 *pylori* infection in Saudi children: a three-year prospective controlled study. *Helicobacter*
30 20(1):56-63. <https://doi.org/10.1111/hel.12172>
- 31 Honar N, Minazadeh A, Shakibazad N, Haghghat M, Saki F, Javaherizadeh H (2016)
32 Diagnostic accuracy of urea breath test for *Helicobacter pylori* infection in children
33 with dyspepsia in comparison to histopathology. *Arq Gastroenterol* 53(2): 108-112.
34 <http://dx.doi.org/10.1590/S0004-28032016000200011>
- 35 Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheimer P,
36 Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC (2017)
37 Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis.
38 *Gastroenterology* 153(2):420-429. <https://doi.org/10.1053/j.gastro.2017.04.022>
- 39 Horiuchi T, Ohkusa T, Watanabe M, Kobayashi D, Miwa H, Eishi Y (2001) *Helicobacter*
40 *pylori* DNA in drinking water in Japan. *Microbiol Immunol* 45(7):515-519.
41 <https://doi.org/10.1111/j.1348-0421.2001.tb02652.x>
- 42 Hulten K, Hans S W, Enroth H, Klein PD, Opekun AR, Gilman RH, Evans DG, Engstrand L,
43 Graham DY, El-Zaatari FA (1996) *Helicobacter pylori* in the drinking water in Peru.
44 *Gastroenterology* 110(4): 1031-1035. <https://doi.org/10.1053/gast.1996.v110.pm8612990>
- 45 IARC 1994. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the
46 Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. IARC Monogr Eval
47 Carcinog Risks Hum 61:1-241.

- 1 Jones N L, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, Czinn S, Gold BD,
2 Guarner J, Elitsur Y, Homan M, Kalach N, Kori M, Madrazo A, Mégraud F,
3 Papadopoulo A, Rowland M; ESPGHAN, NASPGHAN (2017) Joint
4 ESPGHAN/NASPGHAN Guidelines for the Management of *Helicobacter pylori* in
5 Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 64(6):991-1003.
6 <https://doi.org/10.1097/MPG.0000000000001594>
- 7 Kalach N, Gosset P, Dehecq E, Decoster A, Georgel AF, Spyckerelle C, Papadopoulo A,
8 Dupont C, Raymond J (2017) A one-step immune-chromatographic *Helicobacter pylori*
9 stool antigen test for children was quick, consistent, reliable and specific. Acta Paediatr
10 106(12):2025-2030. <https://doi.org/10.1111/apa.13968>
- 11 Kalach N, Gosset P, Dehecq E, Decoster A, Spyckerelle C, Papadopolos S, Dupont C,
12 Raymond J (2015) Usefulness of Gastric Biopsy-Based Real-Time Polymerase Chain
13 Reaction for the Diagnosis of *Helicobacter pylori* Infection in Children. J Pediatr
14 Gastroenterol Nutr 61(3):307-312. <https://doi.org/10.1097/MPG.0000000000000787>
- 15 Kienesberger S, Cox LM, Livanos A, Zhang XS, Chung J, Perez-Perez G, Gorkiewicz G,
16 Zechner EL, Blaser MJ (2016) Gastric *Helicobacter pylori* infection affects local and dis-
17 tant microbial populations and host responses. Cell Reports 14 :1395-1407.
18 <http://dx.doi.org/10.1016/j.celrep.2016.01.017>
- 19 Kikuchi S, Kurosawa M, Sakiyama T (1998) *Helicobacter pylori* risk associated with sibship
20 size and family history of gastric diseases in Japanese adults. Jpn J Cancer Res
21 89(11):1109-1112. <https://doi.org/10.1111/j.1349-7006.1998.tb00504.x>
- 22 Kodaman N, Pazos A, Schneider BG, Piazuolo MB, Mera R, Sobota RS, Sicinschi LA,
23 Shaffer CL, Romero-Gallo J, de Sablet T, Harder RH, Bravo LE, Peek RM Jr, Wilson
24 KT, Cover TL, Williams SM, Correa P (2014) Human and *Helicobacter pylori*
25 coevolution shapes the risk of gastric disease. Proc Natl Acad Sci U S A 111(4):1455-
26 1460. <https://doi.org/10.1073/pnas.1318093111>
- 27 Koletzko S, Richey F, Bontems P, Crone J, Kalach N, Monteiro ML, Gottrand F, Celinska-
28 Cedro D, Roma-Giannikou E, Orderda G, Kolacek S, Urruzuno P, Martinez-Gomez MJ,
29 Casswall T, Ashorn M, Bodanszky H, Mégraud F (2006) Prospective multicentre study
30 on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in
31 Europe. Gut, 55(12), 1711-1716. <http://dx.doi.org/10.1136/gut.2006.091272>
- 32 Kusano C, Gotoda T, Ishikawa, Moriyama M (2017) The administrative project of
33 *Helicobacter pylori* infection screening among junior high school students in an area of
34 Japan with a high incidence of gastric cancer. Gastric Cancer 20(Suppl 1):16-19.
35 <https://doi.org/10.1007/s10120-017-0688-7>
- 36 Lash RH, Genta RM (2016) Routine Anti-*Helicobacter* immunohistochemical staining is
37 significantly superior to reflex staining protocols for the detection of *Helicobacter* in
38 gastric biopsy specimens. Helicobacter 21(6): 581-585. <https://doi.org/10.1111/hel.12315>
- 39 Leal YA, Flores LL, Fuentes-Panana EM, Cedillo-Rivera R, Torres J (2011) 13C-urea breath
40 test for the diagnosis of *Helicobacter pylori* infection in children: a systematic review and
41 meta-analysis. Helicobacter 16(4):327-337.
42 <https://doi.org/10.1111/j.1523-5378.2011.00863.x>
- 43 Makristathis A, Pasching E, Schutze K, Wimmer M, Rotter ML, Hirschl AM (1998)
44 Detection of *Helicobacter pylori* in stool specimens by PCR and antigen enzyme
45 immunoassay. J Clin Microbiol 36(9):2772-2774.
- 46 Malaty HM, Evans DG, Evans DJ Jr, Graham DY (1992) *Helicobacter pylori* in Hispanics:
47 comparison with blacks and whites of similar age and socioeconomic class.
48 Gastroenterology 103(3):813-816. [https://doi.org/10.1016/0016-5085\(92\)90011-M](https://doi.org/10.1016/0016-5085(92)90011-M)

- 1 Malfertheiner P, Mégraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F,
2 Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M,
3 Selgrad M, Suerbaum S, Sugano K, El-Omar EM, European Helicobacter and Microbiota
4 Study Group and Consensus panel (2017) Management of *Helicobacter pylori* infection-
5 the Maastricht V/Florence Consensus Report. Gut 66(1):6-30.
6 <http://dx.doi.org/10.1136/gutjnl-2016-312288>
- 7 Mana F, Vandebosch S, Miendje Deyi V, Haentjens P, Urbain D (2013) Prevalence of and
8 risk factors for *H. pylori* infection in healthy children and young adults in Belgium anno
9 2010/2011. Acta Gastroenterol Belg 76(4):381-385.
- 10 Mastromarino P, Conti C, Donato K, Strappini PM, Cattaruzza MS, Orsi GB (2005) Does
11 hospital work constitute a risk factor for *Helicobacter pylori* infection? J Hosp Infect
12 60:261-268. <https://doi.org/10.1016/j.jhin.2004.12.019>
- 13 McNulty CA, Wise R (1985) Rapid diagnosis of Campylobacter-associated gastritis. Lancet
14 1(8443):1443-1444. [https://doi.org/10.1016/S0140-6736\(85\)91865-3](https://doi.org/10.1016/S0140-6736(85)91865-3)
- 15 Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, Northfield TC (1992)
16 Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. Lancet
17 339:896-897. [https://doi.org/10.1016/0140-6736\(92\)90931-R](https://doi.org/10.1016/0140-6736(92)90931-R)
- 18 Miendje Deyi VY, Bontems P, Vanderpas J, De Koster E, Nitounda R, Van den Borre C,
19 Cadranel S, Burette A (2011) Multicenter survey of routine determinations of resistance
20 of *Helicobacter pylori* to antimicrobials over the last 20 years (1990 to 2009) in Belgium.
21 J Clin Microbiol 49(6):2200-2209. <https://doi.org/10.1128/JCM.02642-10>
- 22 Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A,
23 Bennett C, Forman D (2006) Eradication of *Helicobacter pylori* for non-ulcer dyspepsia.
24 Cochrane Database Syst Rev 19(2)Cd002096.
25 <https://doi.org/10.1002/14651858.CD002096.pub4>
- 26 Momtaz H, Dabiri H, Souod N, Gholami M (2014) Study of *Helicobacter pylori* genotype
27 status in cows, sheep, goats and human beings. BMC Gastroenterol 14:61.
28 <https://doi.org/10.1186/1471-230X-14-61>
- 29 Moosazadeh M, Lankarani KB, Afshari M (2016) Meta-analysis of the prevalence of
30 *Helicobacter pylori* infection among children and adults of Iran. Int J Prev Med 7:48.
31 <https://doi.org/10.4103/2008-7802.177893>
- 32 Morais S, Costa AR, Ferro A, Lunet N, Peleteiro B (2017) Contemporary migration patterns
33 in the prevalence of *Helicobacter pylori* infection: A systematic review. Helicobacter
34 22(3): <https://doi.org/10.1111/hel.12372>
- 35 Moreno Y, Ferrus MA (2012) Specific detection of cultivable *Helicobacter pylori* cells from
36 wastewater treatment plants. Helicobacter 17(5):327-332.
37 <https://doi.org/10.1111/j.15235378.2012.00961.x>
- 38 Mousavi S, Dehkordi FS, Rahimi E (2014) Virulence factors and antibiotic resistance of
39 *Helicobacter pylori* isolated from raw milk and unpasteurized dairy products in Iran. J
40 Venom Anim Toxins Incl Trop Dis 20:51. <https://doi.org/10.1186/1678-9199-20-51>
- 41 Murray LJ, McCrum EE, Evans AE, Bamford KB (1997) Epidemiology of *Helicobacter*
42 *pylori* infection among 4742 randomly selected subjects from Northern Ireland. Int J
43 Epidemiol 26:880-887.
- 44 Nakayama Y, Lin Y, Hongo M, Hidaka H, Kikuchi S (2017) *Helicobacter pylori* infection
45 and its related factors in junior high school students in Nagano Prefecture, Japan.
46 Helicobacter 22(2). <https://doi.org/10.1111/hel.12363>
- 47 Nguyen TVH, Nguyen VB, Binh Phan TT et al (2016) Epidemiology of *Helicobacter pylori*
48 infection in Tay Children in Vietnam. Ann Clin Lab Res 04:1-9. Available from:

- 1 [http://www.aclr.com.es/clinical-research/epidemiology-of-helicobacter-pylori-infection-](http://www.aclr.com.es/clinical-research/epidemiology-of-helicobacter-pylori-infection-in-tay-children-in-vietnam.pH.pylori?aid=17244)
2 [in-tay-children-in-vietnam.pH.pylori?aid=17244](http://www.aclr.com.es/clinical-research/epidemiology-of-helicobacter-pylori-infection-in-tay-children-in-vietnam.pH.pylori?aid=17244)
- 3 Ogihara A, Kikuchi S, Hasegawa A, Kurosawa M, Miki K, Kaneko E, Mizukoshi H (2000)
4 Relationship between *Helicobacter pylori* infection and smoking and drinking habits. J
5 Gastroenterol Hepatol 15(3):271-276.
- 6 Okuda M, Miyashiro E, Koike M, Tanaka T, Bouoka M, Okuda S, Yoshikawa N (2002)
7 Serodiagnosis of *Helicobacter pylori* infection is not accurate for children aged below 10.
8 Pediatr Int 44(4):387-390. <https://doi.org/10.1046/j.1442-200X.2002.01585.x>
- 9 Osaki T, Mabe K, Hanawa T, Kamiya S (2008) Urease-positive bacteria in the stomach
10 induce a false-positive reaction in a urea breath test for diagnosis of *Helicobacter pylori*
11 infection. J Med Microbiol 57(Pt 7):814-819. <https://doi.org/10.1099/jmm.0.47768-0>
- 12 Osaki T, Okuda M, Ueda J, Konno M, Yonezawa H, Hojo F, Yagyu K, Lin Y, Fukuda Y,
13 Kikuchi S, Kamiya S (2013) Multilocus sequence typing of DNA from faecal specimens
14 for the analysis of intra-familial transmission of *Helicobacter pylori*. J Med Microbiol,
15 62:761-765. <https://doi.org/10.1099/jmm.0.053140-0>
- 16 Osaki T, Zaman C, Yonezawa H, Lin Y, Okuda M, Nozaki E, Hojo F, Kurata S, Hanawa T,
17 Kikuchi S, Kamiya S (2018) Influence of intestinal indigenous microbiota on
18 intrafamilial infection by *Helicobacter pylori* in Japan. Front Immunol 9:287.
19 <https://doi.org/10.3389/fimmu.2018.00287>
- 20 Ozaydin N, Turkyilmaz SA, Cali S (2013) Prevalence and risk factors of *Helicobacter pylori*
21 in Turkey: a nationally-representative, cross-sectional, screening with the 13C-Urea
22 breath test. BMC Public Health 13:1215. <https://doi.org/10.1186/1471-2458-13-1215>
- 23 Papiez D, Konturek PC, Bielanski W, Plonka M, Dobrzanska M, Kaminska A, Szczyrk U,
24 Bochenek A, Wierzchos E (2003) Prevalence of *Helicobacter pylori* infection in Polish
25 shepherds and their families. Dig Liver Dis 35(1):10-15.
26 [https://doi.org/10.1016/S1590-8658\(02\)00004-X](https://doi.org/10.1016/S1590-8658(02)00004-X)
- 27 Raj P, Thompson JF, Pan DH (2017) *Helicobacter pylori* serology testing is a useful
28 diagnostic screening tool for symptomatic inner city children. Acta Paediatr 106(3):470-
29 477. <https://doi.org/10.1111/apa.13724>
- 30 Raymond J, Kalach N, Bergeret M, Barbet JP, Benhamou PH, Gendrel D, Dupont C (1996)
31 Evaluation of a serological test for diagnosis of *Helicobacter pylori* infection in children.
32 Eur J Clin Microbiol Infect Dis 15(5):415-417.
- 33 Raymond J, Thiberge JM, Kalach N, Bergeret M, Dupont C, Labigne A, Dauga C (2008)
34 Using macro-arrays to study routes of infection of *Helicobacter pylori* in three families.
35 PLoS One 3(5):e2259. <https://doi.org/10.1371/journal.pone.0002259>
- 36 Rodriguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, Avershina E, Rudi K,
37 Narbad A, Janmalm MC, Marchesi JR, Collado MC (2015) The composition of the gut
38 microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis
39 26:26050. <http://dx.doi.org/10.3402/mehd.v26.26050>
- 40 Rugge M, Meggio A, Pennelli G, Pisciole F, Giacomelli L, De Pretis G, Graham DY (2007)
41 Gastritis staging in clinical practice: the OLGa staging system. Gut 56(5):631-636.
42 <http://dx.doi.org/10.1136/gut.2006.106666>
- 43 Selgrad M, Tammer I, Langner C, Bornschein J, Meißle J, Kandulski A, Varbanova M, Wex
44 T, Schlüter D, Malfertheimer P (2014) Different antibiotic susceptibility between antrum
45 and corpus of the stomach, a possible reason for treatment failure of *Helicobacter pylori*
46 infection. World J Gastroenterol 20(43):16245-16251. <https://doi.org/10.3748/wjg.v20.i43.16245>
47

- 1 Senbanjo I O, Oshikoya KA, Njokanma OF (2014) *Helicobacter pylori* associated with
2 breastfeeding, nutritional status and recurrent abdominal pain in healthy Nigerian
3 children. J Infect Dev Ctries 8(4):448-453. <https://doi.org/10.3855/jidc.3196>
- 4 Shady MM, Fathy HA, Ali A, Galal EM, Fathy GA, Sibaii H (2015) Comparison of serum
5 IgG antibody test with gastric biopsy for the detection of *Helicobacter pylori* infection
6 among Egyptian children. Open Access Maced J Med Sci 3:303-306.
7 <http://dx.doi.org/10.3889/oamjms.2015.062>
- 8 Shu X, Ping, M, Yin G, Jiang M (2017) Investigation of *Helicobacter pylori* infection among
9 symptomatic children in Hangzhou from 2007 to 2014: a retrospective study with 12,796
10 cases. PeerJ 5:e2937. <https://doi.org/10.7717/peerj.2937>
- 11 Strebel K, Rolle-Kampczyk U, Richter M, Kindler A, Richter T, Schlink U (2010) A
12 rigorous small area modelling-study for the *Helicobacter pylori* epidemiology. Sci Total
13 Environ 408(18):3931-3942. <https://doi.org/10.1016/j.scitotenv.2010.03.045>
- 14 Suerbaum S, Michetti P (2002) *Helicobacter pylori* infection. N Engl J Med 347(15):1175-
15 1186. <https://doi.org/10.1056/NEJMra020542>
- 16 Sykora J, Siala K, Varvarovska J, Pazdiora P, Pomahacova R, Huml M (2009) Epidemiology
17 of *Helicobacter pylori* infection in asymptomatic children: a prospective population-
18 based study from the Czech Republic. Application of a monoclonal-based antigen-in-
19 stool enzyme immunoassay. Helicobacter 14(4):286-297.
20 <https://doi.org/10.1111/j.1523-5378.2009.00689.x>
- 21 Thomas J E, Austin S, Dale A, McClean P, Harding M, Coward WA, Weaver LT (1993)
22 Protection by human milk IgA against *Helicobacter pylori* infection in infancy. Lancet
23 342(8863):121. [https://doi.org/10.1016/0140-6736\(93\)91327-I](https://doi.org/10.1016/0140-6736(93)91327-I)
- 24 Torres J, Perez-Perez G, Goodman KJ, Atherton JC, Gold BD, Harris PR, Ia Garza AM,
25 Guarner J, Munoz O (2000) A comprehensive review of the natural history of
26 *Helicobacter pylori* infection in children. Arch Med Res 31(5):431-469.
27 [https://doi.org/10.1016/S0188-4409\(00\)00099-0](https://doi.org/10.1016/S0188-4409(00)00099-0)
- 28 Triantafillidis JK, Gikas A, Hyphantis T, Cheracakis P, Rokkas T, Konstantellou E, Antoniou
29 A, Mallas H, Androulakis G (2002) *Helicobacter pylori* infection in hospital workers
30 over a 5-year period: correlation with demographic and clinical parameters. J
31 Gastroenterol 37(12):1005-1013. <https://doi.org/10.1007/s005350200170>
- 32 Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama
33 K, Sasaki N, Schiempfer RJ (2001) *Helicobacter pylori* infection and the development of
34 gastric cancer. N Engl J Med 345(11):784-789. <https://doi.org/10.1056/NEJMoa001999>
- 35 Urita Y, Watanabe T, Kawagoe N, Takemoto I, Tanaka H, Kijima S, Kido H, Maeda T,
36 Sugawara Y, Miyazaki T, Honda Y, Nakanishi K, Shimada N, Nakajima H, Sugimoto M,
37 Urita C (2013) Role of infected grandmothers in transmission of *Helicobacter pylori* to
38 children in a Japanese rural town. J Paediatr Child Health 49(5):394-398.
39 <https://doi.org/10.1111/jpc.12191>
- 40 Vandenplas Y, Blecker U, Devreker T, Keppens E, Nijs J, Cadranet S, Pipeleers-Marichal M,
41 Goossens A, Lauwers S (1992) Contribution of the ¹³C-urea breath test to the detection
42 of *Helicobacter pylori* gastritis in children. Pediatrics 90(4):608-611.
- 43 Westblom T U, Madan E, Gudipati S, Midkiff BR, Czinn SJ (1992) Diagnosis of
44 *Helicobacter pylori* infection in adult and pediatric patients by using Pyloriset, a rapid
45 latex agglutination test. J Clin Microbiol 30(1):96-98.
- 46 Yahagi E, Khamesipour F, Mashayekhi F, Safarpour Dehkordi F, Sakhaei MH,
47 Masoudimanesh M, Khameneie MK (2014) *Helicobacter pylori* in vegetables and salads:

- 1 genotyping and antimicrobial resistance properties. Biomed Res Int 2014:757941.
2 <http://dx.doi.org/10.1155/2014/757941>
- 3 Zabala Torres B, Lucero Y, Lagomarcino A J, Orellana-Manzano A, George S, Torres JP,
4 O’Ryan M (2017) Review: Prevalence and dynamics of *Helicobacter pylori* infection
5 during childhood. Helicobacter 22(5): <https://doi.org/10.1111/hel.12399>
- 6 Zamani M, Ebrahimitabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J,
7 Derakhshan MH (2018) Systematic review with meta-analysis: the worldwide prevalence
8 of *Helicobacter pylori* infection. Aliment Pharmacol Ther 47(7):868-876.
9 <https://doi.org/10.1111/apt.14561>
- 10 Zhu Y, Zhou X, Wu J, Su J, Zhang G (2014) Risk factors and prevalence of *Helicobacter*
11 *pylori* Infection in persistent high incidence area of gastric carcinoma in Yangzhong city.
12 Gastroenterol Res Pract 2014:481365. <http://dx.doi.org/10.1155/2014/481365>

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

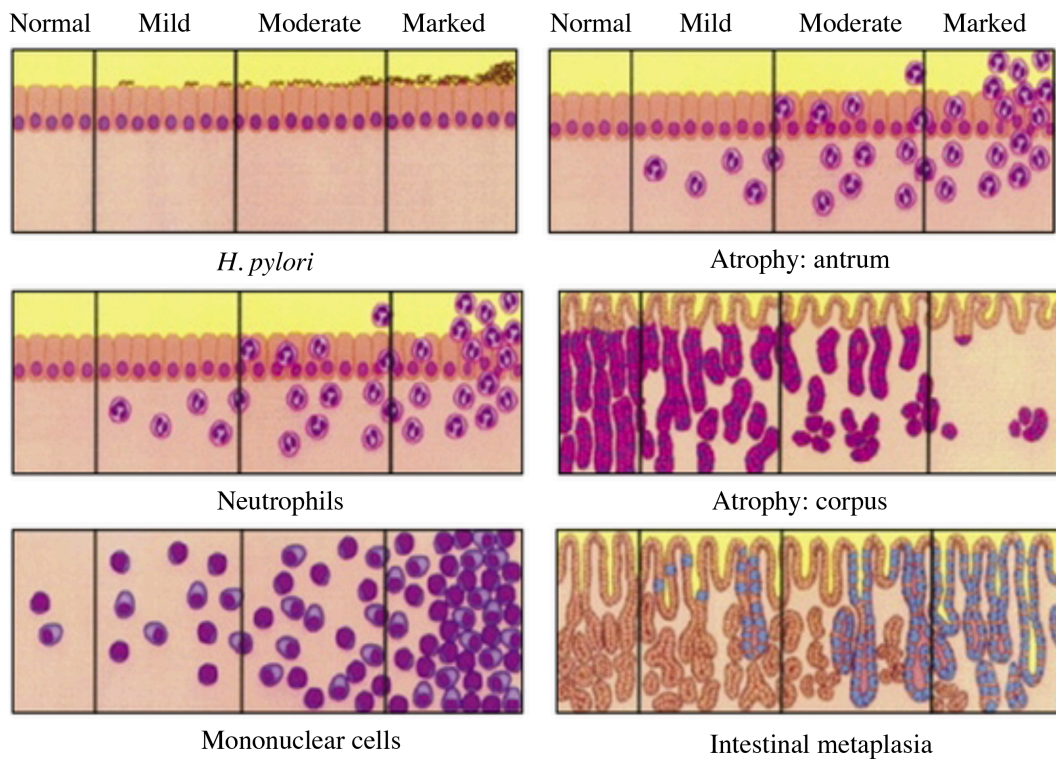
9 **Figure 2 : Risk factors associated to *H. pylori* infection.**

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

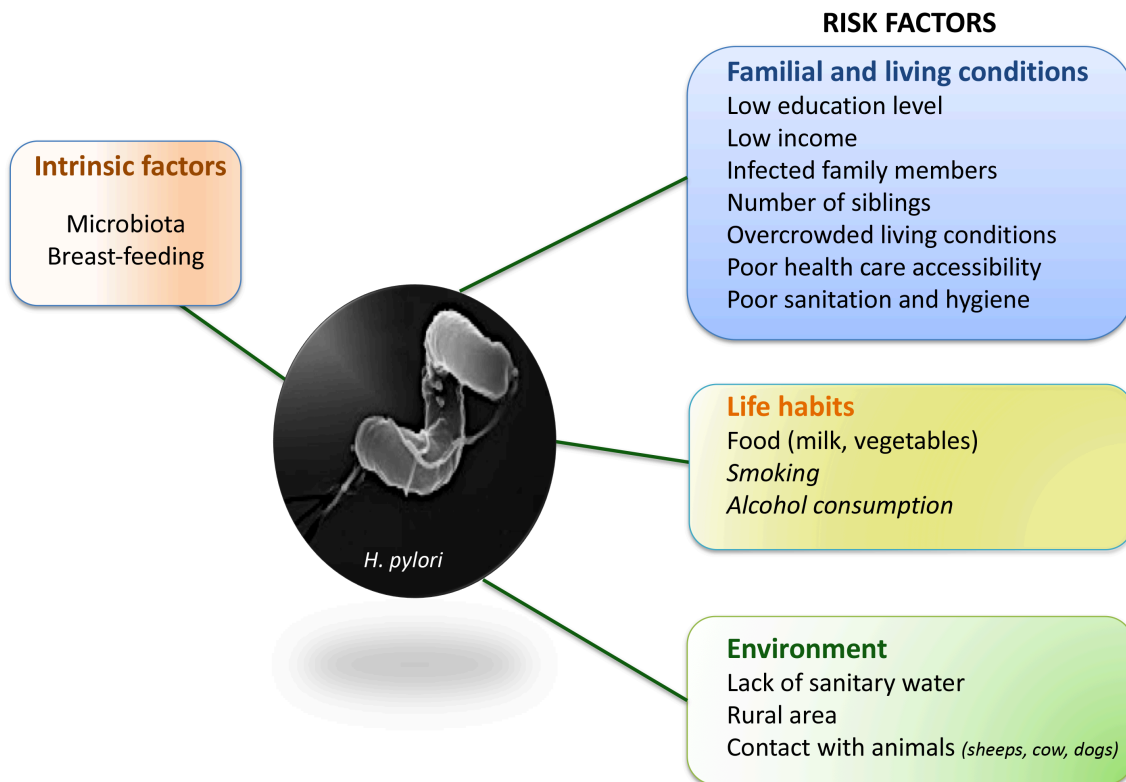
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1

2 **Fig.1**



1

2 **Fig. 2**