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***Helicobacter pylori* Infection in Elderly Patients**

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1. Introduction

Epidemiological studies report an increased rate of gastrointestinal diseases in subjects older than 65 years, and these diseases constitute one of the most frequent indications for medical consultation in this population (Pilotto, 2004). Oesophageal and gastroduodenal diseases, especially *Helicobacter pylori* (*H. pylori*) infection, are frequent in this population since they account for 40% of the total digestive pathologies in the elderly. Even if data in the literature report an increased prevalence of *H. pylori* infection in the elderly, clinical interest remains low. Only 56% of elderly patients hospitalized for peptic ulcers in the United States were tested for *H. pylori* infection, among whom only 73% were then treated (Ofman et al., 2000). However, studies report an increased rate of peptic ulcer disease (PUD) complications and mortality in older patients (1 per million in young adults aged 20 years to 200 per million after 70 years) (Younger&Duggan, 2002). This alarming finding has stimulated further studies on the pathophysiological and clinical aspects of *H. pylori* infection in the geriatric population. Indeed, recent data reported that *H. pylori* chronic infection plays a role in gastric aging, appetite regulation, and possibly extra-digestive diseases such as Alzheimer disease in the elderly.

2. Epidemiology in the elderly

The principal reservoir for *H. pylori* infection appears to be the human stomach, especially the antrum (Megraud, 2003). In developing countries, the oro-fecal route as well as the oro-oral route coexists because of poor socioeconomic and hygienic conditions (Nurgalieva et al., 2002). In developed countries, the oro-fecal transmission has gradually disappeared, leaving the oro-oral route, which is secondary to vomiting and gastro-oesophageal reflux (Megraud, 2003). Even if socioeconomic progress has led to a decrease in the incidence of the infection in developed countries, the prevalence of *H. pylori* infection still remains high in people born at the beginning of the 20th century. In fact, Gause-Nilsson *et al.* (Gause-Nilsson et al., 1998) reported that when cohorts of 70 year old subjects born in 1901-1902 and 1922 were compared, the latter cohort showed a significantly lower *H. pylori* positive serology. This difference in *H. pylori* prevalence may reflect changes in socioeconomic conditions. Epidemiologic studies on elderly people, with a mean age of approximately 70 years, reported a prevalence of nearly 60 percent in asymptomatic subjects (Pilotto et al.,

1996; Regev et al., 1999) and more than 70 percent among the most elderly patients with gastrointestinal diseases (Pilotto, 2001; Pilotto&Salles, 2002). Other studies reported a high prevalence of *H. pylori* infection in the most elderly population, especially in institutionalized old people, with a prevalence ranging from 70 to 85 percent (Regev, Fraser, Braun, Maoz, Leibovici&Niv, 1999). These results can be explained by the mode of transmission of *H. pylori* (oro-fecal or oro-oral), taking into account the promiscuity and living conditions in an institution. Regev *et al.* showed that living in an institution increased the risk of *H. pylori* infection, the prevalence of the infection being positively correlated with the duration of stay (Regev et al., 1999). Nevertheless, even if prevalence increases with age, the prevalence curve appears to be flat and tends to decrease after 85 years (Pilotto&Salles, 2002; Salles-Montaudon et al., 2002). Thus, Neri *et al.* showed that *H. pylori* infection passed from 70 to 50 percent after 90 years (Neri et al., 1996). Two hypotheses can explain this trend. The first hypothesis is an underestimation of *H. pylori* infection, because of frequent chronic atrophic gastritis and frequent current or previous use of antisecretory and antibiotic treatments in this frail population. In a previous work, we showed a lower prevalence of *H. pylori* infection (47.7%) than expected in hospitalized elderly people, which can be explained on one hand by the higher polymedication with repetitive antibiotherapies and on the other hand by more frequent gastric atrophic lesions which offers a less favorable ground for *H. pylori* (Salles-Montaudon et al. 2002). The second hypothesis is a premature death of *H. pylori* infected subjects due to various comorbidities, e.g., gastric cancer, peptic ulcer diseases (PUD) and possibly other diseases such as cardiovascular diseases. Based on the data from the PAQUID Cohort study ("Personnes Agées Quid?" which was designed to enrol and follow-up elderly subjects randomly selected in the South-Western France⁴), we recently evaluated the impact of *H. pylori* infection on the mortality rate in a population of subjects older than 65 years. The follow-up of 605 subjects over 15 years, after adjustment for age, gender, and cardiovascular comorbidity, showed that an *H. pylori* infection was not a risk factor for mortality (HR=1.2, 95% CI [0.94; 1.52]) (Salles et al.).

3. *H. pylori* infection and peptic ulcer disease

The elderly are particularly susceptible to peptic ulcer disease (PUD) and complications due to their higher *H. pylori* prevalence and use of non-steroidal anti-inflammatory drugs (NSAIDs) (Bhala&Newton, 2005; Chow et al., 1998; Jones&Hawkey, 2001). Even if it is well known that the incidence of gastric ulcers increases in elderly people, little is known about gastric mucosal healing alterations during ageing. Newton et al. reported that gastric ageing induces gastric frailty, characterized by a reduction in protective factors, i.e., mucus layer, prostaglandin levels, mucosal growth, and gastric blood flow, and a higher susceptibility to aggressive factors, i.e., NSAID and *H. pylori* infection (Newton, 2004). Age-related changes could occur as a result of increased exposure to exogenous factors, alterations in the secretion of endogenous aggressive factors, or changes in the production or repair of the mucus bicarbonate layer, the primary barrier against acid and pepsin digestion. The increased risk of severe complications in this population (haemorrhage, gastric perforation) is likely to mask important early symptomatic signs which make PUD treatment difficult in the elderly (Kemppainen et al., 1997). Most of the studies suggested that ulcer pain is less common in this age group. Indeed, the diagnosis of PUD is usually delayed, because symptoms are not easily detected in this population. Typical pain is often absent; only one third of people older than 60 years experience painful symptoms (Seinela&Ahvenainen,

2000). In geriatric practice, anorexia and malnutrition frequently represent alarm symptoms and lead to gastroduodenal endoscopy. Endoscopic exploration, which is most of the time well tolerated in elderly patients, allows a diagnosis in more than 50 percent of the cases (Van Kouwen et al., 2003). Another contributing factor to PUD in the elderly is a high usage of NSAIDs and/or aspirin. Pilotto et al. showed that NSAID use independently increases the risk of peptic ulcer and ulcer bleeding. This risk increases with age in a linear manner, and increases further in the event of comorbidities and polymedication which are common in this population (Pilotto et al., 2003). *H. pylori* infection also independently increases the risk of PUD in the elderly. Clinical studies reported that approximately 50 to 70 percent of elderly peptic ulcer patients are *H. pylori* positive (Pilotto, 2001). The short- and long-term studies performed on elderly patients demonstrated that treatment of *H. pylori* infection in patients with peptic ulcer resulted in ulcer healing in over 95 percent of the patients and significantly improved clinical outcomes, including a decrease in recurrence (Pilotto&Salles, 2002). With regard to the respective responsibility of the two risk factors previously mentioned (AINS, *H. pylori*) in PUD, studies confirmed that both independently and significantly increase the risk of PUD and ulcer bleeding.

4. *H. pylori* infection and gastric aging

The ageing stomach is usually described in terms of the occurrence of gastric atrophic lesions. Thus, a wide range of studies reported an increased prevalence of atrophic gastritis in elderly patients, with rates ranging between 50 to 70% in patients over eighty (Sachs et al., 2003; Younger&Duggan, 2002). Only a few studies provided results on intrinsic gastric ageing and most were animal studies. In contrast, most of the literature reported the strong role played by chronic *H. pylori* infection in the occurrence of atrophic gastric lesions. The discovery of *H. pylori* chronic infection has cast a doubt on the reality of the physiological gastric ageing process which is now considered as a process of "pathological gastric ageing". Since the discovery of the strong role of this chronic gastric infection in the development of a gastric atrophy and PUD, we actually consider that most of the observed changes in the stomach that appear during ageing are, in fact, the result of environmental causes, such as chronic infection, nutritional, and pharmacological factors. These environmental factors may participate in inducing gastric frailty with impaired mucosal defence.

4.1 Chronic atrophic gastritis

A series of studies, mainly from Japan, has focused on the long-term effects of *H. pylori* infection and its role in the development of the histological changes that occur with ageing, i.e., atrophic gastritis (Salles, 2007). In a large multicenter trial, authors reported that both atrophic gastritis and intestinal metaplasia were strongly associated with *H. pylori* infection and not with ageing *per se* (Asaka et al., 2001). Interventional prospective studies reported that *H. pylori* eradication induces a significant reduction of inflammatory and atrophic gastric lesions (Ito et al., 2002; Kokkola et al., 2002). Kokkola et al. reported that advanced atrophic gastritis may improve and heal after *H. pylori* eradication in elderly subjects (Kokkola et al., 2002). They followed prospectively 22 elderly men (55–69 years of age) with *H. pylori* infection and atrophic corpus gastritis. During a 7.5-year period prior to eradication therapy, no significant changes were observed in the mean atrophy and IM scores. However, after *H. pylori* eradication, a significant improvement occurred in the mean

histological Sydney system score of inflammation (from 2.2 to 0.5), atrophy (from 2.2 to 1.2) and IM (from 1.6 to 1.1). These findings are in agreement with the results of another study carried out in 132 subjects aged from 34 to 68 years (mean age 50 years) with multifocal (nonautoimmune) atrophic gastritis. Six years after cure of *H. pylori* infection, a significant improvement in antral atrophy was detected in subjects who received anti-*H. pylori* treatment, the effect being greater among those who were free of infection at the end of the trial (Ruiz et al., 2001). Since the response to treatment was similar in patients of different ages, we may assume that the cure of *H. pylori* infection is as recommended in elderly patients with gastric mucosal modifications as it is for young and adult patients. During gastric ageing, histological modifications are frequently observed leading to physiological gastric disturbances. Thus, a high prevalence of chronic atrophic gastritis is frequently observed in the gastric mucosa of elderly people (Ofman et al., 2000; Pilotto, 2004). These histological lesions lead to hypochlorhydria with a risk of bacterial overgrowth in the proximal digestive tract and intestinal malabsorption.

4.2 Gastric acid secretion

Between 1920 and 1980, many studies reported a significant reduction in gastric acid secretion with age. The majority of these studies was retrospective and did not take into account the presence of possible gastric atrophic lesions (Salles, 2007). More recent studies including elderly patients showed that there is no change in acid secretion with age, whereas others even showed an increase in acid secretion. Those studies that demonstrate hyposecretion in elderly patients offer chronic *H. pylori* infection and atrophic gastritis of the oxyntic mucosa as a reasonable explanation. Shih et al. found that gastric acid secretion does not change with age (Shih et al., 2003). Feldman et al. studied gastric acid secretion in elderly patients and found that basal acid output and peak acid output did not correlate with age (Feldman & Cryer, 1998). Similarly, Lijima et al., reported that gastric acid secretion was well preserved irrespective of ageing, however it seemed to increase with ageing in the *H. pylori*-negative subjects (Lijima et al., 2004). The decline in gastric acid secretion in *H. pylori*-positive patients depends on both an increasing prevalence of fundic atrophic gastritis and inflammatory cytokines, i.e., interleukin (IL) IL-1 β and TNF- α , which are known to inhibit parietal cells. The mechanism promoting the increase in acid secretion with ageing is unknown. However, since the alteration of acid secretion by the inflammation of oxyntic mucosa can be ignored in the *H. pylori*-free stomach, two main possibilities could be considered: one is an increase in the total parietal cell mass with age, and the second is an increase in the reactivity of parietal cells. Because the previous studies failed to find any change in parietal cell mass with ageing, the second possibility is more likely.

4.2.1 Gastrointestinal bacterial overgrowth

Only a few clinical studies investigated the prevalence of gastrointestinal bacterial overgrowth in older healthy people, and most of the results showed that bacterial overgrowth occurs rarely during the normal process of gastric ageing, but is rather an iatrogenic process (antisecretory drugs) in the elderly. Mitsui *et al.* performed a study (Mitsui et al., 2006) and included healthy and disabled older people, aged over 70 years. They reported no bacterial overgrowth among healthy patients, but only in disabled or frail older people. Parlesak *et al.* also performed a study in older adults using a hydrogen breath test (Parlesak et al., 2003) and reported a 15.6% prevalence of small bowel bacterial overgrowth. They showed that PPI treatments played a role in increasing the prevalence of

positive breath tests in older adults, which was associated with lower body weight, lower body mass index, lower plasma albumin concentration, and higher prevalence of diarrhea. The pH of gastric acid and bacterial counts in the stomach showed a close correlation. In normal subjects the gastric pH is usually below pH 4, a critical level for protection against enteric pathogens, and the stomach is virtually sterile. At a pH of 4–5 bacteria from the saliva are present in the stomach. A pH greater than 5 allows bacterial, viral and protozoan pathogens to survive and enteric bacteria can be found in the stomach. Other drugs which decrease acid production are anticholinergic drugs and tricyclic antidepressant drugs. In geriatrics, malnutrition is one of the clinical consequences of bacterial overgrowth, and antibiotic treatment may lead to the improvement of the anthropometric parameters of these patients (Lewis et al., 1999).

4.2.2 Vitamin B12 deficiency

Cobalamin or vitamin B12 deficiency is common in elderly patients (Dali-Youcef&Andres, 2009). The Framingham study demonstrated a prevalence of 12% among elderly people living in the community. Other studies focusing on elderly sick and malnourished people living in institutions have suggested a higher prevalence of 30–40%. The main causes of cobalamin deficiency include food-cobalamin malabsorption, pernicious anaemia, and insufficient nutritional vitamin B12. Dietary causes of deficiency are limited to elderly people who are already malnourished with lower albumin level, such as frail elderly patients with severe co morbidities (Salles-Montaudon et al., 2003). First described by Carmel in 1995, food-cobalamin malabsorption is frequent in elderly people, and is characterized by the inability of the body to release cobalamin from food or intestinal transport proteins, particularly in the presence of hypochlorhydria, where the absorption of 'unbound' cobalamin is normal (Carmel et al., 2003). Food-cobalamin malabsorption is caused primarily by chronic atrophic gastritis. In fact, Andres et al, reported in a recent meta-analysis, that cobalamin deficiency, other than those caused by nutritional deficiency, can be treated by oral administration of vitamin B12 in the form of cyanocobalamin (free cobalamin) (Andres et al., 2009). An evidence-based analysis by the *Vitamin B12 Cochrane Group* also supports the efficacy of oral cobalamin therapy. In this analysis, serum vitamin B12 levels increased significantly in patients receiving either oral vitamin B12 alone or patients receiving both oral and intramuscular treatment (Vidal-Alaball et al., 2005). Other factors that contribute to food-cobalamin malabsorption in elderly people include chronic carriage of *H. pylori* and intestinal microbial proliferation, situations in which cobalamin deficiency can be corrected by antibiotic treatment, long-term ingestion of antiacids such as H₂-receptor antagonists and PPI, and biguanides (metformin) (Dali-Youcef&Andres, 2009). Sipponen et al, reported normalization of vitamin B12 levels after *H. pylori* eradication (Sipponen et al., 2003).

5. *H. pylori* infection and gastric cancer

Gastric carcinoma and gastric MALT lymphoma have been causally associated with *H. pylori*, and the bacterium has been categorized as a group I carcinogen by the International Agency for Research on Cancer (IARC). The incidence of gastric cancer increases with age worldwide. However, the association between *H. pylori* infection and gastric cancer might have been underestimated due to possible clearance of the infection in the course of disease development, especially among older patients who generally have more severe mucosal

atrophy and intestinal metaplasia in the stomach. Recently, a new analytical investigation to minimize a potential underestimation of the association of *H. pylori* with gastric cancer was performed on Western populations [60]. Applying various more stringent exclusion criteria to minimize a potential bias from this source increased the odds ratio (95% confidence interval) of non-cardia gastric cancer from 3.7 to 18.3 for any *H. pylori* infection, and from 5.7 to 28.4 for *cagA*-positive *H. pylori* infection (Brenner et al., 2004). A possible mechanism to explain the link between *H. pylori* infection and gastric carcinoma is inflammation which increases the risk of mutations. Many of the mediators and byproducts of inflammation are mitogenic and mutagenic. Release of pro-inflammatory cytokines, reactive oxygen species and upregulation of Cox-2 all contribute to an intragastric environment conducive to neoplastic transformation. The mechanisms involve direct DNA damage, inhibition of apoptosis, subversion of immunity, and stimulation of angiogenesis. In addition, chronic inflammation in the gastrointestinal tract is also known to affect proliferation, adhesion and cellular transformation. There is also evidence of a direct carcinogenic effect of *H. pylori* per se on the gastric mucosa. As mentioned before, the type 4 secretion system encoded by the *cag* PAI allows the bacterium to inject molecules into the epithelial cells. The CagA protein is one of them. It acts on numerous cell effectors disturbing cell physiology leading to several proneoplastic processes, e.g. activation of growth factor receptors, increased proliferation, evasion of apoptosis, sustained angiogenesis and cell dissociation, and tissue invasion.

6. Impact of *H. pylori* infection on appetite regulation

The results showed that the expression of leptin and ghrelin peptides decreased both in the presence of an *H. pylori* infection and in the presence of atrophic gastritis lesions. The possible role of *H. pylori* infection in the regulation of appetite in the elderly is an interesting new research topic. Studies reported that *H. pylori* eradication appeared to improve certain nutritional parameters, i.e., body mass index (BMI), and albumin (Azuma et al., 2002; Fujiwara et al., 2002). Kamada et al. recently showed a significant increase in the BMI after *H. pylori* eradication among patients suffering from gastric ulcers, with a parallel increase in triglyceride and cholesterol levels (Kamada et al., 2005). In geriatric practice, anorexia and weight loss are often the only symptoms of PUD and are signs warranting endoscopic exploration. It is also crucial to investigate *H. pylori* infection in such cases. Studies performed on adults indicate that inflammatory cytokines may cause anorexia by inducing variations in circulating gastrointestinal hormones, neuropeptides, and NO, all of which can alter food intake (Chapman, 2004; Morley, 2001). Recently, we showed that chronic inflammation in the gastric mucosa affects the expression of gastric satiety inducible peptides such as leptin and ghrelin (Salles et al., 2006). Recent evidence suggests that, in humans and rats, leptin is secreted not only from adipose tissue but also from the gut (Bado et al., 1998). Studies indicate that gastric inflammation induced by *H. pylori* infection raises gastric leptin expression which then induces satiety and lower BMI (Azuma et al., 2001; Konturek et al., 2001). Ghrelin is a newly discovered peptide which is produced mainly in the stomach and is involved in the control of food intake and energy homeostasis in both humans and rodents (Kojima et al., 1999). In a recent study, authors reported that a cure of *H. pylori* infection increased plasma ghrelin, which in turn led to an increased appetite and weight gain (Nwokolo et al., 2003). Consequently, chronic gastric inflammation may induce variations in the expression of both leptin and ghrelin and may play a role in the

pathophysiology of anorexia in elderly patients. In a study on frail elderly patients over 80 years old, we showed that the presence of *H. pylori* chronic gastritis induced a decrease in both leptin and ghrelin gastric production; this finding may, in fact, be due to the high prevalence of atrophic lesions observed in this particular population (Salles et al., 2006). Furthermore, the presence of *H. pylori* chronic gastritis was negatively correlated to the caloric ratio and the body mass index of these aged patients. The decrease in plasmatic and gastric levels of the strong orexigen, ghrelin, could explain the lack of appetite and the malnutrition of aged people who have chronic gastritis lesions due to *H. pylori*

7. *H. pylori* infection and Alzheimer's disease

The risk factors identified for dementia are often inaccessible to intervention (age, gender, genetic). New hypotheses have recently been suggested, such as the possible relationship between *H. pylori* infection and dementia via inflammatory mechanisms, both pro-oxidant and carential. Indeed, in addition to two case-control studies pointing out an association between *H. pylori* infection and Alzheimer disease (Kountouras et al., 2006; Malaguarnera et al., 2004), an interventional study has shown that *H. pylori* eradication positively influences Alzheimer disease manifestations, especially cognitive decline (Kountouras et al., 2009). Preliminary results of a cohort study conducted in our laboratory concluded that *H. pylori* infection was a significant risk factor for developing Alzheimer disease. One of the hypothesis is that *H. pylori* infection could act as a trigger in the genesis or in the accumulation of Alzheimer disease lesions via cerebral hypoperfusion due to atherosclerosis, or via an exacerbation of neuroinflammation.

8. Diagnosis of *H. pylori* infection in the elderly

Diagnosis of *H. pylori* infection remains difficult in elderly patients because of the characteristics of this population.

8.1 Non-invasive methods

The advantage of these methods is that they are global tests, i.e., *H. pylori* can be detected even if the patchy distribution of the bacteria, when gastric atrophy is present, precludes their histological detection.

8.1.1 Serology

Generally speaking, *H. pylori* immunoglobulin G (IgG) antibodies appear 2 to 3 weeks following infection, and slowly decrease after *H. pylori* eradication. In adulthood, the performance of serology (ELISA) shows 85 to 95 percent sensitivity and 80 to 95 percent specificity (Granberg et al., 1993). Even if most of the epidemiologic studies included serology to detect *H. pylori* infection in the elderly, data concerning the performance of this test remain contradictory for this population. Some authors consider that there is a risk of over-estimating infection in the elderly when using serology, because antibodies remain present for months or even years after *H. pylori* eradication (Kosunen et al., 1992). Indeed, in this population, the prevalence of *H. pylori* infection is significantly higher when detected by serology than by histology. Studies reported that in *H. pylori* positive patients with atrophic body gastritis, after eradication therapy, the time delay concerning the decrease in *H. pylori* IgG did not always correlate with the reduction in gastric inflammation (Kosunen et al.,

1992). This suggests that, in patients with atrophic body gastritis, serology alone may not be valid for assessing the efficacy of eradication treatment. Liston et al. showed that nearly one third of their study patients had positive serology without signs of active *H. pylori* infection (Liston et al., 1996). In addition, other authors reported that serology may not be useful in determining successful eradication post-therapy in the elderly, because of a great heterogeneity in the decrease in IgG antibody titer (6 months or more) (Kosunen et al., 1992). On the contrary, some authors consider that serology may underestimate the infection in the elderly. This could be explained by a possible lack of antibody response due to a frequent immunodeficiency diagnosed in frail elderly people. In fact, immunodeficiency may be the consequence of protein malnutrition which occurs in more than 30 percent of the elderly population (Burns, 2004; Salles-Montaudon et al., 2002). The infection could also be underestimated because of the characteristics of this elderly population, often hospitalized and treated with antibiotics for recurrent urinary tract or pulmonary infections which can induce false negative results.

Immunoblot (Western blot) is another serologic method useful in the elderly, for the detection of antibodies directed against particular antigenic proteins of *H. pylori* (CagA, VacA, urease A and B). Pilotto et al. showed that the presence of a CagA positive *H. pylori* infection was independently correlated with atrophic gastritis and intestinal metaplasia in the elderly (Monteiro et al., 2002; Pilotto et al., 1998).

8.1.2 ¹³Carbon-Urea Breath Test

The ¹³carbon-urea breath test (¹³C-UBT) has an excellent diagnostic performance including the post-therapy determination of successful *H. pylori* eradication. The principal disadvantage of this method is the need for specific equipment which associates gas chromatography and mass spectrometry. In the elderly, this test has the advantage of being easily performed with a minimum of cooperation from the patient, and it is very well tolerated. Pilotto et al. demonstrated the excellent performance of this test on elderly patients, with a diagnostic accuracy of 97.9%. They found it useful even for patients with severe cognitive impairment (Pilotto et al., 2000). In a recent study performed on hospitalized patients older than 85 years, we reported that almost one-third of the *H. pylori*-positive patients would have remained undetected without this test, including treated patients (PPIs and antibiotics), or patients with chronic corpus atrophic gastritis [16]. Some studies reported the risk of an overestimation of *H. pylori* infection when using this test on the elderly. This could be explained by a hypochlorhydria due to gastric atrophy, which allows gastric colonization by urease-producing bacteria present in the mouth, oropharynx, and small intestine and decreases the specificity of the test (Chen et al., 2000). Certain situations can, to the contrary, involve an underestimation of *H. pylori* diagnosis in older subjects. Among these various cases, a past gastric resection may decrease the amount of urea present in the stomach, leading to an insufficient *H. pylori* detection.

8.1.3 Stool test

One of the formats of this test is a microwell-based immunoassay (HpSA), which detects *H. pylori* antigens present in human stools (Vaira et al., 1999). This test has a good diagnostic performance and can be easily carried out in routine. The test's lower sensitivity in the elderly can be explained by the higher frequency of chronic constipation in this group. Indeed, the passage of the bacteria into the colon may be prolonged, leading to a degradation of *H. pylori* antigens and jeopardizing their detection. This has been shown

experimentally in stools spiked with *H. pylori*. Moreover, studies have shown that PPI treatment decreases the accuracy of HpSA by increasing the gastric pH and suppressing *H. pylori* colonization (Monteiro et al., 2001). The HpSA test also presents the disadvantage of being more difficult to carry out in this very old population, mainly for practical reasons, in dependent or demented older subjects (Salles-Montaudon et al., 2002).

8.2 Invasive methods

Most of the time, older patients have diagnostic indications for upper gastrointestinal endoscopy, i.e., chronic anemia, dysphagia, epigastralgia, etc. Biopsy sampling per endoscopy permits the detection of *H. pylori* infection by urease test, histological analysis, culture or PCR.

8.2.1 Biopsy urease test

There are several tests available based on the the urease activity of *H. pylori* present in biopsy specimens, among which are the CLO test® and the PyloriTek®. In the elderly, studies reported a lower sensitivity of these tests (57%) compared to histology or serology (Abdalla et al., 1998). As stated previously, the lower sensitivity can be explained by multiple treatments for various infections, and frequent gastric atrophic lesions which may induce a hostile environment for the bacterium.

8.2.2 Histology

In the elderly, the performance of this test increased when biopsy specimens were taken from two areas of the stomach, i.e., the antrum and the body. Indeed, chronic gastric atrophy may induce gastric hypochlorhydria which may in turn reduce *H. pylori* colonization in the antrum. In the elderly, a histological analysis should not be the only diagnostic method for *H. pylori* infection, because of its lower sensitivity as previously stated.

Nevertheless, this method presents the advantage of evaluating the morphological parameters of the gastric mucosa, using the Sydney System classification suggested in 1990 by Price et al. (Price, 1991). The revised classification made in 1994 in Houston is now widely accepted (Genta&Dixon, 1995). These criteria are studied and quantified as either mild, moderate or severe: activity, inflammation, atrophy, intestinal metaplasia, and the presence of *H. pylori* infection. Given the increased incidence of malignancy in the elderly population, histology has become mandatory.

8.2.3 Culture

Microbiological examination of biopsy specimens is considered as the reference technique. Culture provides unique information which is helpful in the management of *H. pylori* infection, in particular the strain's susceptibility to antimicrobial agents (Mégraud, 1996). Concerning all of the "invasive methods", they may underestimate *H. pylori* infection in the elderly because of the frequent antibiotic and PPI treatments, and also the high prevalence of chronic atrophy lesions.

8.2.4 Molecular methods

Molecular diagnosis of *H. pylori* infection presents a real interest. PCR detection of *H. pylori* in gastric biopsies offers very sensitive and accurate results in a short time. Many protocols

have been developed for targeting different genes with specific primers for *H. pylori*. Recently, realtime PCR assays were developed allowing simultaneous detection and quantification as well as the determination of antibiotic susceptibility and genotyping of *H. pylori* (Oleastro et al., 2003).

9. Indications for treatment in geriatrics

9.1 Peptic ulcer disease

The short- and long-term studies performed on elderly patients indicate that treatment of *H. pylori* infection in patients with peptic ulcers results in healed ulcers in over 95% of the patients, and significantly improves the clinical outcome, reducing ulcer recurrence, and histological signs of ulcer-associated chronic gastritis activity [13,86]. It is, thus, strongly recommended to test and treat *H. pylori* infection among the elderly presenting peptic ulcers. Pilotto et al. showed that the rate of peptic ulcer relapse in eradicated older patients was 2 percent versus 42 percent in those non-eradicated (Pilotto, 2001).

9.2 Atrophic chronic gastritis

As stated previously, *H. pylori* eradication induces a decrease in the severity of gastric inflammation, atrophy and intestinal metaplasia (Kokkola et al., 2002). The Maastricht 2-2000 Consensus Report recommends treating patients with atrophic gastritis (Malfertheiner et al., 2002).

9.3 Non-ulcer dyspepsia

The effectiveness of *H. pylori* eradication in patients with non-ulcer dyspepsia is still a matter of debate. A study carried out on a geriatric population showed a significant improvement in symptoms of functional dyspepsia in 70% of the patients two months after eradication (Pilotto et al., 1999). However, the long-term benefit was not studied.

9.4 Gastroesophageal reflux disease

The relationship between *H. pylori* infection and the clinical evolution of gastroesophageal reflux disease has not yet been clarified in elderly subjects (Kountouras et al., 2004; Kountouras et al., 2006). In a study carried out on elderly patients with esophagitis, Pilotto et al. reported that healing of esophagitis after a 2 month treatment with PPIs was similar in *H. pylori*-positive and *H. pylori*-negative patients (Pilotto et al., 2002). Moreover, eradication therapy did not accelerate the clinical response to short-term PPI therapy among these patients. *H. pylori* eradication is thus not recommended for elderly patients with gastroesophageal reflux disease.

9.5 Use of non-steroidal anti-inflammatory drugs

It is now established that most peptic ulcers are caused by *H. pylori* or NSAIDs. Studies showed that *H. pylori* eradication is not sufficient in preventing ulcer bleeding in high-risk NSAID users (Chan et al., 2002; Lai et al., 2003; Pilotto et al., 2000a). It does not enhance the healing of peptic ulcer in patients taking antisecretory therapy who continue to take NSAIDs. However, PPI was superior to the eradication of *H. pylori* in preventing recurring bleeding in patients who are taking NSAIDs.

Among patients with *H. pylori* infection and a history of upper gastrointestinal bleeding who are taking low-dose aspirin, the eradication of *H. pylori* is equivalent to treatment with

omeprazole in preventing recurrent bleeding (Chan et al., 2001). In conclusion, there is no clear proof which supports the systematic eradication of *H. pylori* in elderly patients treated with short- or long-term aspirin and/or NSAID drugs.

10. *H. pylori* eradication in geriatrics

Many clinical trials demonstrated that PPI-based triple therapies for 1 week, as recommended by the Maastricht 2-2000 Consensus Report, were highly effective in the elderly population (Pilotto&Malfertheiner, 2002). *H. pylori* eradication is more effective in elderly people compared to younger individuals. Studies performed on elderly patients also showed that a reduction in the PPI dosage, i.e. omeprazole (20 mg) and pantoprazole (40 mg), from twice daily to once daily did not influence the cure rates of triple therapies consisting of either PPI plus clarithromycin (250 mg b.i.d.) and metronidazole (500 mg b.i.d.), or PPI plus clarithromycin (250 mg b.i.d.) and amoxicillin (1 g b.i.d.) (Pilotto et al., 2001; Pilotto&Malfertheiner, 2002; Pilotto&Salles, 2002).

Bad compliance, which is frequently observed in elderly subjects, and *H. pylori* resistance to antibiotics, are the major reasons for treatment failure in elderly patients (Pilotto&Salles, 2002). Studies reported that metronidazole resistance decreased with age (OR for patients over 60 years = 0.63, 95% CI = 0.48-0.80) and was higher in females than in males (Pilotto&Salles, 2002). The optimal strategy for second-line therapy associates PPI with amoxicillin and metronidazole or PPI with tetracycline and metronidazole, with a recommendation to increase the duration of treatment (10 to 14 days) as well as the metronidazole doses. Concerning the poor compliance in older patients, the use of structured patient counselling and follow-up may have a significant effect on *H. pylori* cure rates and should be part of therapy management.

11. Conclusion

The strongest prevalence of *H. pylori* infection in the elderly as well as the role of *H. pylori* in the occurrence of gastric lesions, in particular ulcer diseases, gastric precancerous lesions, and gastric cancer, render the diagnosis and the eradication of *H. pylori* capital in this population. However, studies evaluating the prevalence, diagnosis and treatment of this infection are still few concerning this population, especially in frail patients older than 80 years.

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

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