Introduction

Warren and Marshall’s [1] discovery of Helicobacter pylori in 1983 revolutionized the clinical approach to some of the commonest gastroduodenal pathologies. The prevalence of H. pylori infection increases with age worldwide, reaching levels of 40–60% in asymptomatic elderly subjects [2–4] and over 70% in elderly patients with upper gastrointestinal diseases [5, 6]. The aim of the present review is to summarize the most recent progress in the treatment of H. pylori infection in elderly subjects, and to attempt to answer the following two questions: (i) whom to treat and (ii) how to treat.

Whom to treat?

Peptic ulcer disease

Clinical studies involving peptic ulcer patients older than 65 years have reported H. pylori positivity rates ranging from 50 to 78% [5, 7–11]. Currently, there is agreement that the cure of H. pylori infection is of proven benefit for patients with H. pylori-associated ulcer disease [12]. The National Institute of Health in the United States [13] as well as the European H. pylori Study Group (EHPSG) [14] have published consensus reports recommending the cure of H. pylori infection in all patients with gastric or duodenal ulcer disease [12]. The few controlled, short-term studies (1 or 2 months of follow-up) performed in elderly patients have demonstrated that the treatment of H. pylori infection in patients with peptic ulcer disease healed ulcers in high percentages (over 95%) [16–18], improved symptomatology in over 85% of patients [18] and significantly reduced the histological activity of ulcer-associated chronic gastritis [17, 18]. Very recently, a 1-year follow-up study performed in elderly patients with peptic ulcer [19] showed that the eradication of H. pylori infection improved clinical outcome, reducing ulcer recurrences, symptomatology and the histological signs of ulcer-associated chronic gastritis activity.

On the basis of these data, the cure of H. pylori infection is strongly recommended in elderly patients with H. pylori-associated peptic ulcer disease.

Gastric lymphoma and carcinoma

A recently published case series reported a 60–70% remission rate in gastric mucosa-associated lymphoid tissue lymphoma after H. pylori eradication [20]; the remission remained stable for more than 1 year [21]. Since remission of the disease subsequent to H. pylori therapy seems to occur irrespective of the patient’s age [22], H. pylori eradication is also strongly recommended in elderly patients.

Several studies have reported that H. pylori infection is associated with gastric cancer [23, 24], gastric atrophy and intestinal metaplasia [25, 26], the last two of which may be early precursors to gastric cancer [27]. Very recently, an association of cytotoxin-associated gene A (CagA)-positive strains of H. pylori with gastric atrophy and intestinal metaplasia has been reported in elderly patients [28], confirming the hypothesis that an infection with these H. pylori strains may be catalytic in inducing gastric changes which can evolve into malignancies [29, 30]. The finding that geographical...
variations in gastric cancer are not fully explained by the prevalence of *H. pylori* infection [31] or by CagA positivity [32] is surely due to the multifactorial pathogenesis of gastric cancer [31]. Of course, for ethical reasons, the clinical course of *H. pylori* infection cannot be left unchecked in patients with documented premalignant lesions. Therefore, the EHPSG consensus [33] strongly recommended *H. pylori* eradication in patients with advanced forms of gastritis, such as erosive or hypertrophic gastritis, intestinal metaplasia and gastric atrophy, and also after resection of early gastric cancer or premalignant lesions [34].

The EHPSG Maastricht Consensus guidelines [14] recommend the cure of *H. pylori* infection in positive subjects with a family history of gastric cancer, with gastric surgery for peptic ulcer and in patients on long-term antisecretory treatment for reflux oesophagitis to avoid the progression of *H. pylori*-induced atrophic gastritis [35]. No studies have been performed in older age groups to evaluate the possibility of age-specific differences in disease outcome with *H. pylori* eradication. Thus, at present, such indications remain uncertain in elderly subjects.

In agreement with the Maastricht Consensus report, we do not currently recommend *H. pylori* eradication for large-scale cancer prevention in asymptomatic people with no known risk factors or in relatives of infected patients.

**Non-ulcer dyspepsia**

Meta-analysis studies have shown a higher prevalence of *H. pylori* infection in patients affected by non-ulcer dyspepsia compared with controls [36]. However, the clinical efficacy of anti-*H. pylori* treatments in patients with non-ulcer dyspepsia is still debated. Two studies which did not include elderly subjects reported either a symptomatic benefit [37] or a lack of effect [38] of treating *H. pylori* infection in subjects with non-ulcer dyspepsia. A recent study in elderly patients documented an improvement of symptomatology in 70% of patients with non-ulcer chronic gastritis 2 months after treatment [18]. However, no studies have yet evaluated the efficacy of *H. pylori* therapy on symptomatology after longer periods of follow-up.

**Gastro-oesophageal reflux diseases**

The relationship between *H. pylori* infection and gastro-oesophageal reflux diseases is complex and still undefined [39]. No evidence of association between *H. pylori* infection and reflux oesophagitis has yet been reported in elderly subjects [40]. A recent study performed in 214 elderly patients with oesophagitis reported that 50% of patients were infected with *H. pylori*; the presence of the bacterium was significantly associated with lower severity of oesophagitis [41]. However, at baseline and during acid suppressive therapy, *H. pylori* did not influence acid reflux and symptoms in subjects with Barrett’s oesophagus [42]. No consistent change in gastro-oesophageal acid reflux was reported after *H. pylori* eradication in patients with mild or moderate oesophagitis [43].

Recent studies suggest that gastro-oesophageal reflux diseases might arise de novo following cure of *H. pylori* in peptic ulcer patients [44, 45]. A study of 150 elderly patients with *H. pylori*-positive peptic ulcer or chronic gastritis reported that the post-treatment persistence of symptoms (with an increase in the percentages of heartburn and acid regurgitation) was significantly associated with oesophagitis and not with *H. pylori* infection [18]. A number of possible mechanisms might account for the phenomenon of rebound reflux after *H. pylori* cure [39]. Because a variable proportion of peptic ulcer patients have coexistent gastro-oesophageal reflux diseases [46], the phenomenon could be explained, at least in part, by the unmasking of pre-existing disease [39].

**Users of non-steroidal anti-inflammatory drug (NSAIDs)**

*H. pylori* infection in elderly people is associated with an increase in NSAID-related gastric and duodenal ulcers, but not with a higher prevalence of upper gastrointestinal bleeding [47]. Indeed, the role of *H. pylori* infection in NSAID-related gastroduodenal damage in elderly subjects is not yet well established. Two recent studies in patients aged between 20 and 82 years with NSAID-related ulcers, who were treated for 6 months with omeprazole, ranitidine or misoprostol, reported that a positive test for *H. pylori* infection was associated with a significantly greater likelihood of remaining in remission [48, 49]. In contrast, in two case-control studies performed in elderly patients, NSAID use and *H. pylori* infection were shown to be independent and unrelated risk factors for gastroduodenal bleeding [50, 51].

Treatment efficacy studies which evaluated the effect of *H. pylori* eradication on the risk of NSAID-related gastroduodenal lesions have reported controversial results. In one study, eradication of *H. pylori* before NSAID therapy reduced the occurrence of NSAID-related peptic ulcers after 2 months [52]. Other studies failed to find a significant difference in cumulative peptic ulcer recurrence rates between chronic NSAID users who remained *H. pylori*-positive and those who were free from *H. pylori* after 6 months of follow-up [53, 54]. To date, the only study performed in elderly patients reported that the use of proton pump inhibitors, such as pantoprazole, reduced the occurrence of acute NSAID-related gastroduodenal damage more effectively than the eradication of *H. pylori* infection [55]. At present, therefore, no clear evidence supports testing and treatment of *H. pylori* infection in elderly NSAID users for prevention of drug-related gastroduodenal damage [56, 57].
Extradigestive diseases

A scientific debate has arisen about the possible association of H. pylori infection with extradigestive diseases, principally cardiovascular diseases [58], but also idiopathic chronic urticaria [59], autoimmune thrombocytopenia [60] and other immunological, skin and liver disorders [61]. The few studies performed in elderly populations failed to find any association between H. pylori infection and coronary heart disease [62, 63] or extracardiac atherosclerosis [64]. To date, the presence of extradigestive diseases in subjects is not an indication for the testing or treatment of H. pylori infection.

Subjects living in nursing homes

For many people, advanced age coincides with institutional living and, thus, with an increased risk of infections. The seroprevalence of H. pylori infection in asymptomatic elderly people living in a nursing home for at least 5 years was reported in one study to be 86%. This was not significantly different from the 82% serological prevalence among asymptomatic elderly subjects living at home [65]. No significant correlation was observed between seropositivity and length of institutional stay, cognitive functions or self-sufficiency [66]. Moreover, H. pylori infection was not related to modification of nutritional status [65, 66] or gastric function parameters [65]. However, a high antibody titre correlated significantly with raised levels of pepsinogen C, suggesting that elderly institutionalized subjects are at high risk of H. pylori infection [67] and that such an infection, in asymptomatic elderly subjects, may induce an inflammatory gastric condition [65]. Employees of institutes for the intellectually disabled, especially those with a long duration of employment and who have close physical contact with patients, are at increased risk of developing H. pylori infection [68]. However, no specific hygienic or behavioural measures are currently recommended for minimizing H. pylori transmission among elderly and professional people in nursing homes.

How to treat?

Treatment regimens

In 1997, the EHPSG’s Maastricht Consensus guidelines recommended that eradication regimens should be simple, well tolerated and achieve an eradication rate of over 80% on an intention-to-treat analysis [69]. The therapeutic regimens which have been shown to satisfy these criteria involve 7 days of therapy with a standard dose of a proton pump inhibitor (i.e. omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg, twice daily), plus two of the following antibiotics: clarithromycin, amoxycillin and a nitroimidazole (metronidazole or tinidazole).

One controlled study performed in elderly patients showed that a triple therapy for 1 week with 20 mg or 40 mg omeprazole daily plus 250 mg metronidazole four times daily and 250 mg clarithromycin twice daily was highly effective (an 84% eradication rate; 95% CI, 73–95 on intention-to-treat analysis) [17]. Excellent cure rates were also obtained with 1 week of 30 mg lansoprazole twice daily in combination with 250 mg of clarithromycin twice daily and 250 mg of metronidazole four times daily (86% eradication rate; 95% CI, 76–96), or in combination with 1 g of amoxycillin twice daily plus 250 mg clarithromycin twice daily (82% eradication rate; 95% CI, 71–93) or with 1 g of amoxycillin twice daily plus 250 mg metronidazole four times daily (80% eradication rate; 95% CI, 69–91) [18]. In another study, no significant differences in eradication rates (78%, 80% and 81% respectively on intention-to-treat analysis), symptomatology or histological gastritis activity were found by varying the proton pump inhibitor: 20 mg omeprazole twice daily, 30 mg lansoprazole twice daily or 40 mg pantoprazole daily in combination with 1 g amoxycillin twice daily and 250 mg metronidazole four times daily [70]. In contrast, dual therapies with omeprazole plus clarithromycin or azithromycin [17] or with lansoprazole plus amoxycillin [16] did not give satisfactory cure rates. Particularly relevant for geriatric patients was the finding that concomitant diseases and concomitant treatments did not influence the efficacy of anti-H. pylori therapy [71]. Furthermore, in the same study, the baseline H. pylori density and gastritis activity of patients successfully and unsuccessfully treated for H. pylori infection were not significantly different [71].

Triple proton pump inhibitor-based therapies have been proven to be well tolerated, with only 5–9% of patients reporting side effects and less than 4% of patients having discontinued therapy due to these effects [17, 18]. Such a low rate of side effects and the reported high rate of patient compliance are probably due to the short (1-week) duration and the low dosage of both antibiotics and proton pump inhibitors [72–74].

Indeed, reports of severe side effects of anti-H. pylori therapy in elderly patients were related only to the use of tetracycline [75], to high doses (500 mg three times daily) of clarithromycin [76] or to quadruple therapy including metronidazole, amoxycillin, H2-blockers and bismuth subsalicylate [77].

Some studies have recently demonstrated that a 7-day co-administration of ranitidine bismuth citrate plus clarithromycin and metronidazole [78] or clarithromycin and tetracycline [79] may be effective and well-tolerated regimens for the eradication of H. pylori. At present, however, since no studies have evaluated dual or triple ranitidine bismuth citrate-based therapies specifically in elderly patients, no recommendation can be made regarding the role of this agent in elderly populations.
Resistance of *H. pylori* to antibiotics

Resistance of *H. pylori* to antibiotics included in current eradication regimens is one of the major reasons for treatment failure [80]. This problem may be particularly relevant in elderly patients for two reasons: (i) the prevalence of drug consumption (including antibiotics) is higher in this population and (ii) compliance and dosage (two important factors which affect resistance) are probably lower in elderly than in young or adult populations. Unfortunately, few studies have concentrated on this topic in this group. A recent study performed in a group of subjects aged 25–90 years (mean age 67.7) showed that resistance to metronidazole was 17.2%, and to clarithromycin 6.9% [81]. Metronidazole resistance was associated with a significantly lower eradication rate in comparison with susceptible *H. pylori* strains, while macrolide resistance had no significant clinical relevance, probably due to the low number of patients who presented with such a resistance [81].

The only study performed to date in elderly patients reported a low prevalence of amoxycillin resistance (<2%) [82], confirming that such a resistance is clinically of little relevance [83]. However, because several studies have reported that *H. pylori* antibiotic resistances may change with time even within the same population, principally due to the emergence of secondary resistances to either metronidazole and clarithromycin after treatment of *H. pylori* or other infective diseases, a continuous surveillance of *H. pylori* susceptibility to antibiotics at the national or regional level would be needed to make valuable recommendations as to the most effective primary treatment in a specific geographic area [81].

Post-therapy evaluation of patients

Elderly patients with a diagnosis of peptic ulcer (especially gastric ulcer), gastric mucosa-associated lymphoid tissue lymphoma or severe gastritis should be evaluated by endoscopy and gastric mucosal histology after completion of anti-*H. pylori* therapy. Most experts agree that this evaluation must be carried out at least 1 month after completion of therapy in order to minimize false-negative results.

Elderly patients with the more mild to moderate forms of chronic gastritis may be evaluated after therapy by a non-invasive test. Very recently, the $^{13}$C-breath test demonstrated in elderly subjects significantly higher sensitivity (100%), specificity (95.7%) and diagnostic accuracy (98%) than serology (IgG anti-*H. pylori* antibodies). Furthermore, it was shown to be unaffected by potential co-variables such as cognitive function, disability, co-morbidity and co-treatments [84]. In agreement with a previous study demonstrating the low sensitivity (62%) and specificity (56%) of serology in monitoring *H. pylori* treatment in elderly people [71], this suggests that the routine use of serum IgG antibodies for the monitoring of *H. pylori* infection should not be a recommended clinical practice since this test does not accurately reflect the elderly patient’s true gastric *H. pylori* status [5, 85, 86].

Regarding elderly patients who are still *H. pylori*-positive after treatment, no studies have been performed to clarify whether it is more clinically useful and/or cost-effective to re-treat immediately with a second-line therapy [87] or to identify specifically any antibiotic *H. pylori* resistance by performing a repeat endoscopy and the necessary microbiological assays [88]. For these cases, availability, expense and a clinical perspective which incorporates a total vision of the patient and his or her health needs may suggest to the physician the most effective means to ensure ideal management [89].

Key points

- Eradication of *H. pylori* infection is strongly recommended in elderly patients with *H. pylori*-positive peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma and advanced forms of gastritis, as well as in patients after resection of early gastric cancer or premalignant lesions.
- Eradication of *H. pylori* infection is advisable in patients with troublesome dyspeptic symptoms and documented chronic active gastritis, intestinal metaplasia or gastric atrophy.
- Further study is needed to give clear indications of the value of eradication for patients who have mild to moderate non-ulcer dyspepsia or gastro-oesophageal reflux diseases or who use non-steroidal anti-inflammatory drugs.
- To date, *H. pylori* eradication is not indicated for asymptomatic patients, for elderly subjects living in nursing homes or for patients with extradigestive diseases.
- One-week proton pump inhibitor-based triple therapies are highly effective and well tolerated in elderly patients.
- The effect of anti-*H. pylori* therapy may be evaluated by endoscopy (with gastric histology) or by non-invasive methods: the $^{13}$C-breath test is currently the best non-invasive diagnostic method for monitoring of *H. pylori* infection in elderly people.

References


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