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Helicobacter pylori and gastric cancer: a critical approach to who really needs eradication

Elias Kouroumalis[1,2]*, Ioannis Tsomidis[2], Argyro Voumvouraki[3]

[1]Department of Gastroenterology, PAGNI University Hospital, University of Crete School of Medicine, 71500 Heraklion, Greece
[2]Laboratory of Gastroenterology and Hepatology, University of Crete School of Medicine, 71500 Heraklion, Greece
[3]1st Department of Internal Medicine, AHEPA University Hospital, 54621 Thessaloniki, Greece

***Correspondence:** Elias Kouroumalis, Department of Gastroenterology, PAGNI University Hospital, University of Crete School of Medicine, 71500 Heraklion, Greece. kouroumi@uoc.gr
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Abstract

It is generally accepted that eradication of *Helicobacter pylori* (*H. pylori*) infection may reduce the risk of the development of gastric cancer. Recommendations for global generalized tests and treat all individuals detected positive for *H. pylori* infection are currently proposed. However, the bacterium is commensal and harmless for the vast majority of the infected population. Moreover, eradication may have detrimental consequences in several groups of patients. In the present review, the current epidemiological data and recommendations for eradication in connection with the possible beneficial effects of the colonization with *H. pylori* in diseases such as asthma and allergies or chronic gastro-intestinal disorders such as inflammatory bowel disease and Barrett' esophagus are presented the problems with increasing antibiotic resistance were also examined. Specific groups of patients where eradication of *H. pylori* may be necessary and endoscopic surveillance is advised were identified. Finally, based on the paradox of high *H. pylori* prevalence and low gastric risk as reported for areas of Africa, Asia, South America, and Greece, alternatives that may replace the widespread eradication of *H. pylori* with equal if not better results and more prudent use of the available financial resources are proposed. Mediterranean diets and alcohol and smoking reduction are among the well documented alternatives.

Keywords

Helicobacter pylori, eradication, gastric cancer, Mediterranean diet

Introduction

Gastric cancer (GC) remains one of the leading causes of cancer death worldwide, despite the considerable decline in developed countries. Eradication of *Helicobacter pylori* (*H. pylori*), a class 1 human carcinogen, has been strongly recommended as an efficient and cost-effective policy to reduce the risk of GC among asymptomatic individuals by establishing population-based test-and-treat programs. The damage of the

gastric epithelium caused by *H. pylori* may evolve to gastric adenocarcinoma. Corpus atrophy, intestinal metaplasia (IM), and mucosal dysplasia are considered as pre-neoplastic lesions and are associated with *H. pylori* colonization. However, the different levels of GC risk and different clinical situations are unclear. New, updated data on the global epidemiology of *H. pylori* infection and GC are accumulated and there is a strong concern that target populations should be identified and treated instead of the universal eradication. There is a need for eradication confirmatory tests including identification of individuals for endoscopy and endoscopic surveillance. However, the extensive use of antibiotics for eradication of *H. pylori* has raised concerns, and the possible harmful consequences after eradication have also been expressed.

The purpose therefore, of this review was to present recent data on the relation of *H. pylori* with GC and the current recommendations of eradication. More importantly, we analyzed the arguments against the widespread global eradication programs and proposed the groups that may be benefited from *H. pylori* eradication. Moreover, an alternative approach to GC prevention was presented.

An overview of *H. pylori* epidemiology and pathogenesis

H. pylori is a gram-negative, spiral-shaped bacterium belonging to the Proteobacteria, order Campylobacterales, family Helicobacteriaceae.

Epidemiological data

Its extensive prevalence in the general population reaching up to 80% is characterized by geographical distribution and the socio-economic status of the population [1]. Prevalence of *H. pylori* infection is decreasing not only in developed countries but also in the Russian Federation where a prevalence of 78% was reported in 2017 [2] and only 40% in a recent publication [3]. High *H. pylori* prevalence was found in countries of Latin America. In Chile, high prevalence was identified in newborns during the first month after birth. In Canada, the indigenous populations in the Arctic were found to have higher infection rates compared to non-indigenous inhabitants [4]. The same was true in the city of Amsterdam, in the Netherlands. Ethnic minority groups were significantly more infected with *H. pylori* compared to the indigenous Dutch population [5].

Large geographical variance in prevalence was reported in a meta-analysis with data from 62 countries. The highest pooled prevalence of 70% was found in Africa and the lowest of 24.4% in Oceania. Among countries, the lowest prevalence of 18.9% was found in Switzerland and a very high 87.7% was reported for Nigeria. Based on these findings, it was estimated that almost 4.4 billion individuals were infected by *H. pylori*. The global prevalence in adults has declined from an overall 50–55% to a recent 43%. However, this is not the case in Asia, Latin America, and the Caribbean [2, 6, 7].

It is generally accepted that *H. pylori* infection is a life-long event, when individuals are infected. However, spontaneous clearance of 15.5% was reported in children during a 20-year follow-up. Interestingly, strain concordance was detected in 56% between mother and offspring and 0% between father and offspring [8–10].

The most serious problem with *H. pylori* infection is the association with the development of GC. Non-cardia adenocarcinomas have been linked to *H. pylori* with a very high odds ratio (OR) up to 21.0 [11]. In general, *H. pylori* is estimated to be associated with 36.8% of GCs out of the 2.2 million cancers linked to infections. In 2018, 89% of the 850,000 cases of non-cardia GC cases and 73% of non-Hodgkin gastric lymphomas were associated with *H. pylori* infections [12]. A recent meta-analysis [13] reported data from 32 countries on the prevalence of GC in *H. pylori*-positive patients. The highest prevalence was observed in America (18.06%) and the lowest in Africa (9.52%). Among countries, Japan had the highest pooled prevalence (90.90%) whereas in Sweden the lowest prevalence (0.07%) was observed. The overall risk of GC development from birth to old age is 1.87% in males and 0.79% in females while the incidence for GC have considerably decreased over the last 75 years. However, the mortality remains high in countries such as Japan, China, and Chile [14]. Environmental and genetic factors also modify the lifetime risk of GC [6, 15–

17]. Genetic factors, housing conditions, and dietary habits may be responsible for the increased risks in East Asian populations [18–20].

A global average annual percentage reduction of 2.1% has been reported. The incidence rates of GC are expected to constantly decline through 2030 in most countries except Ecuador and Lithuania [21]. It should be noted however, that even in countries such as the UK where GC is not a major problem any more, it is one of the leading causes of cancer-associated death [22, 23].

Pathogenetic mechanisms in GC development

H. pylori infection is responsible for chronic destruction of the acid-secreting glands of the stomach, evolving to atrophic gastritis (AG) and IM [24, 25]. However, only 2–3% of infected patients develop GC, and 0.1% will develop mucosa-associated lymphoid tissue (MALT) lymphoma [26, 27]. Most investigators accept that there is a point of no return during gastric carcinogenesis independent of *H. pylori* status. This is reported to be associated with IM and dysplasia [28]. The penetration of *H. pylori* penetration into the epithelial mucus layer activates the phagocytic cells macrophage and neutrophils of the mucosa. They produce reactive oxygen species (ROS) and nitric oxide (NO) to defend against the invaders [29]. However, all *H. pylori* strains are capable of detoxifying ROS, producing catalase and superoxide dismutase. And arginase that reduces NO production [30]. In addition, the bacterial survival is increased by inducing mitochondria-dependent apoptosis of macrophages.

It has been suggested that certain strains of *H. pylori* are more dangerous than others to initiate GC. These strains are producing proteins such as vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA) [11, 31, 32]. The effects of VacA on cells include induction of vacuoles, induction of apoptotic cell death, induction of autophagy, and effects on several immune cells [33]. CagA on the other hand, has a direct oncogenic effect leading to AG and GC [34, 35]. CagA is responsible for aberrant activation of several oncogenic proteins such as rat sarcoma protein (Ras), β-catenin, phosphatidylinositol 3-kinase (PI3K), and others [36] triggering thus the oncogenic stress response (OSR). One of the central regulators of the OSR is the ADP-ribosylation factor (ARF) protein. ARF protein induces apoptosis and permanent cell cycle arrest by increasing stability and activation of p53 protein [37, 38]. Ubiquitin ligases such as apoptosis regulatory protein Siva (SIVA1) that controls ARF protein degradation is inhibited by *H. pylori* [39, 40]. Interestingly, in contrast to VacA, CagA inhibits apoptosis activating several antiapoptotic pathways. Importantly, CagA impairs the antiapoptotic activity of the tumor suppressor factor p53 through degradation of the p53 protein [38, 41]. CagA phosphorylation also regulates the degradation of ARF tumor suppressor (p14ARF).

Additional proteins that increase the risk of GC development, are the outer membrane proteins (OMPs) such as the blood-group antigen-binding adhesin (BabA) and the outer inflammatory protein A (OipA). BabA binds to epitopes that increase production of cytokines involved in cell proliferation. OipA activates β-catenin and the PI3K-protein kinase B (AKT) signaling pathway [20, 42].

An additional mechanism of *H. pylori* pathogenicity is the release of outer membrane vesicles (OMVs) by certain strains, consisting of a variety of cellular constituents. OMVs, may be either harmful or defensive [43]. OMVs from *H. pylori* induce the secretion of interleukin-8 (IL-8) by gastric epithelial cells and activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) pathways, modulating thus cell proliferation and cancer initiation [44]. This hypothesis was supported by the finding that the presence of OMVs is significantly increased in the gastric juice of GC patients compared to normal controls [45]. The biologically active compounds of OMVs also, promote apoptosis of gastric epithelial and immunocompetent cells such as macrophages [46]. Furthermore, *H. pylori*-induced oxidative stress activates the intrinsic pathway of apoptosis leading to cell death. As mentioned before, VacA also promotes apoptosis. Thus, excessive apoptosis will result in cell mass loss, as observed in gastric ulcers [47] being therefore the background of the association of *H. pylori* with peptic ulceration.

Additionally, *H. pylori* activates the innate immune response. At the initial stages of the infection *H. pylori* releases several pathogens associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS)

and flagellin that are recognized by several innate pattern recognition receptors (PRRs). *H. pylori* PAMPs are weak activators of the host receptors allowing a chronic infection. Some other PAMPs such as ADP-heptose, nucleic acids, and OMVs are not yet fully studied in detail [48].

Apoptosis inhibition is an important element in carcinogenesis. Equally important is the process of autophagy. Autophagy is a survival mechanism at the initial stages of cellular insult. Autophagy polymorphisms were associated with GC in Chinese patients, and 28 autophagy related genes (*ATGs*) were down-regulated in *H. pylori*-infected gastric cells. The presence of the *ATG16L1* rs2241880 increased the risk of GC while the presence of the immunity-related GTPase M (*IRGM*) rs4958847 decreased the GC risk [49]. The *ATG16L1* rs2241880 G-allele is associated with the progression of gastric premalignant lesions and cancer possibly due to the modulation of *H. pylori*-induced endoplasmic reticulum (ER) stress [50–52]. Experimental evidence suggests that at the initial stages of *H. pylori* infection autophagy regulation is different during evolution of the infection [53, 54]. It has been shown that during the acute infection, autophagy is initiated through secretion of VacA and in turn degrades VacA and CagA. However, at the chronic stage VacA and CagA restrict autophagy inhibiting their degradation, and increasing the damage of the epithelial cells [55].

Arguments in favor of *H. pylori* eradication and GC

Multidrug resistant *H. pylori* strains are constantly emerging worldwide [56, 57]. Therefore, it is important to demonstrate to what extent GC can be prevented by *H. pylori* eradication. Many studies have addressed this point.

In a recent meta-analysis [58], there was evidence that eradication of *H. pylori* reduces the incidence of GC and death rates from GC in otherwise healthy asymptomatic individuals, but there was no adequate evidence to indicate a reduction in all-cause mortality. No extrapolation to other populations can be made, since six out of seven trials were conducted in Asian populations. A further meta-analysis from the same group included data from 10 randomized trials with more than 8,000 *H. pylori*-infected patients. It was calculated that over 8 million disability-adjusted life-years were gained after *H. pylori* eradication. Moderate evidence suggested that eradication reduced the incidence of GC and GC-related mortality in East Asia [59]. These findings were corroborated by an additional meta-analysis from the same area [60, 61]. Treatment for *H. pylori* infection should be attempted after endoscopic resection of early GC to prevent metachronous GC [62, 63]. This has been verified by a recent meta-analysis where the occurrence of metachronous GC after *H. pylori* eradication was similar to an *H. pylori*-negative group [64].

One of the problems facing the eradication regimens in the prevention of GC is that most studies are either retrospective or meta-analyses. A prospective, randomized controlled trial from Korea on participants with a first-degree relative with GC showed that *H. pylori* eradication resulted in a 55% reduction in GC appearance. When eradication failed a 27% higher risk of GC was found [65].

Treatment of *H. pylori* infection in AG

Asymptomatic individuals with *H. pylori*-positive AG are the most important source for *Helicobacter* transmission [66]. According to certain guidelines [67–69], all *H. pylori*-positive individuals should receive eradication treatment including therefore AG positive patients. The rationale is that eradication will reverse the atrophic and metaplastic changes and stop the Correa cascade of evolution to the point of no return [61, 70, 71]. However, GC appears even after successful eradication, leading to a debate for the point of no return. The presence of IM is the current point beyond which the eradication strategy may not prevent GC compared to earlier stages of the infection [28]. The potential benefits of eradication are probably dependent on the degree of atrophic damage already present at the time of eradication [67, 68]. This is supported by a recent single-center retrospective study, where diffuse-type GC development was associated with the degree of gastric atrophy at the time of the initial diagnosis after a long follow-up (mean 7.1 years). The standardized incidence ratio for diffuse GC was negligible in mild gastric mucosal atrophy and 10.9 in moderate atrophy. GC developed more frequently in the second decade of follow-up, suggesting

that endoscopic surveillance should be continued for at least 10 years after *H. pylori* eradication in high-risk areas [72].

The reversibility of AG after *H. pylori* eradication is still debatable [73]. The most objective way to answer the question requires histological confirmation preferably by using the histological staging systems of operative link for gastritis assessment (OLGA) and operative link for gastric IM assessment (OLGIM) [74, 75]. Endoscopic scoring systems such as the proposed by Kimura and Takemoto can be used, but they require considerable experience and cannot substitute for histological confirmation [76]. A recent meta-analysis of 12 studies showed that eradication improved AG in the corpus but not in the antrum. Moreover, there was no evidence for a significant resolution of IM either in the corpus or in the antrum [77]. Two other meta-analyses reported significant improvement of gastric atrophy after eradication, but no improvement of IM [28, 78]. Controversial results were obtained in a long-term follow-up study where IM in the antrum and corpus improved after successful eradication [79]. A very recent study with 69 participants from arctic territories of Canada reported that compared to baseline precancerous gastric pathology was substantially lower at follow-up. Eradication of *H. pylori* led to reduction of severity of active and AG. No data on IM is reported in this study [80].

Recurrence after eradication of *H. pylori* is an important problem in GC prevention. The recurrence rate is higher in countries with higher prevalence of *H. pylori* infection and lower socio-economic conditions [81, 82]. High recurrence rates were reported in areas such as Alaska, Vietnam, and Bangladesh [83–85]. The overall annual recurrence rates after *H. pylori* treatment, but without mass eradication policies, was 4.3%, according to a meta-analysis [81]. There are many reasons for recurrence [81, 82]. Recurrence can be due to the reappearance of the original strain or to the reinfection by a different strain [86, 87]. The recurrence is also dependent on the pattern of eradication program. In a study without mass eradication, the annual recurrence was 7% per person-year [88], but only 1% in the small community in the Matsu Islands, where almost 82% of the population participated in the eradication program [89].

An additional problem with *H. pylori* eradication is the administration of antibiotic-based regimens in children as children very rarely suffer serious consequences particularly in the west. The matter is still open to debate [90]. An interesting possibility for children is the hypothesis that administration of probiotics reduces *H. pylori* adhesion to gastric epithelial cells and prevents colonization. Further clinical trials are needed [91]. Probiotic co-supplementation to antibiotic therapies is reported in several studies in adults. A substantial reduction in resistance genes for several antibiotics was reported for *Saccharomyces boulardii* supplementation during *H. pylori* eradication [92]. Furthermore, a meta-analysis showed that probiotic administration increased the *H. pylori* eradication rate [93]. However, the significance of gut microbiota alterations after probiotic administration is not clear. Long-term follow-up studies to clarify possible detrimental consequences of the probiotic intervention in *H. pylori* eradication are required before recommendations can be made [94].

The recommendations for testing for the presence of *H. pylori* are intimately connected to eradication recommendations. A Chinese consensus panel suggested screening and eradication in all high-risk populations [95]. On similar grounds, it was suggested that test and eradication should be applied to all individuals with IM although the suggestion is based on moderate quality of evidence. The authors also urge for more widespread availability of antimicrobial susceptibility tests in the United States [96, 97]. Patients with peptic ulcers are regularly tested as part of the standard of care recommendations. However, nearly 20% of all hospital admissions with bleeding peptic ulcers were not tested for *H. pylori* particularly those who were admitted in an ICU. Failing to test and eradicate resulted in twice as high re-bleeding or death rates when compared to tested patients [98].

Symptomatic improvement as a surrogate indication for successful eradication should not be advocated and there is a strong recommendation that a non-invasive test should be used particularly in those where eradication has been administered for GC prevention [27].

H. pylori eradication costs

The quality-adjusted life year (QALY) is the quantification of the disease burden including both the quantity and quality of life (QoL). However, a number of questions on the interpretation of derived QALY remain unresolved [99]. This is particularly true for studies in children where the relative cost-effectiveness (cost per QALY gained) in many diseases and populations, should be faced with extreme caution [100]. The derivative of the cost divided by QALY gained is called incremental cost effectiveness (ICER). It is also used for assessment of the cost of diseases but its use is not without problems [101].

There have been several attempts to estimate the cost of eradication strategies in *H. pylori* infection. Only recent papers were reviewed, as financial situations are changing rapidly over time. A previous consensus report has estimated that it would need 125 individuals to be treated to prevent one case of GC in countries with high GC incidence. A higher number would be needed in countries with low incidence making eradication possibly not necessary in these populations. Yet, the consensus recommendation was in favor of the test-and-treat policy [68].

The cost-effectiveness of population-wide eradication strategy has produced controversial results in different populations. In Denmark, a country with low incidence of *H. pylori* prevalence neither improvement of QoL nor cost-effectiveness were demonstrated [102]. Markov models from a high prevalence country such as China, showed that the population-wide screening was cost-effective in prevention of GCs in asymptomatic individuals [103, 104]. As the majority of *H. pylori* infections is acquired during childhood, eradication policies in young adults are now implemented in Japan [105]. A meta-analysis based on eight studies reported that the lowest ICER calculated was 1,230 US dollars per life-year gained and 1,500 US dollars per QALY. However, the cost-effectiveness analysis was dependent on many factors that make direct comparisons difficult [106]. A recent study from China compared the ICERs of three treatment strategies, namely the annual, triennial, and five-yearly *H. pylori* screening, and concluded that screening for *H. pylori* in asymptomatic populations is cost-effective. The significance of the frequency of screening was inferior compared to increased participation [107]. In Japan, an eradication strategy was more cost-effective compared to endoscopic screening provided acceptance to pay a threshold of 50,000 US dollars per QALY gained according to Monte Carlo simulations. They concluded that over a lifetime, an eradication strategy, may prevent 4.47 million GC cases, and may save 319,870 lives from GC [108]. In the special population of eradicated *H. pylori*, it was suggested that biennial endoscopy is the cost-effective screening for mild to moderate atrophy and annual endoscopy for those with severe atrophy compared to no screening [109].

There are two points that should be commented on when costs are concerned. The first is that all estimations are based on mathematical Markov models and Monte Carlo simulations. However, acceptable these methods may be, they are based nonetheless on many assumptions that may prove to be erroneous in real-time evaluations. The second point is that no model has taken into account the consequences of the recent SARS-CoV-2 pandemic that crippled many health systems and may have changed spending priorities and the willingness to pay thresholds in many countries.

Is *H. pylori* the only pathogen responsible for GC?

There is evidence that *H. pylori* may not be the only microbe responsible for the development of GC as suggested by the fact that *H. pylori* is reduced in areas of tumor tissue. [110–112]. The normal gastric microbiota has extensive diversity. Proteobacteria, Firmicutes, Actinobacteria, Bacteroides, and Fusobacteria are the most prevalent phyla. In *H. pylori* colonization of the gastric mucosa, the most abundant organism, accounting for 40–90% of the gastric microbiota is *H. pylori* [113]. *H. pylori* colonization interferes with the gastric microbiota and a crosstalk between *H. pylori* and gastric commensal bacteria may be involved in *H. pylori*-related carcinogenicity [114]. *H. pylori* inhibits the colonization of other bacteria, decreasing the diversity of gastric microbiota. *H. pylori*-positive individuals have a higher abundance of Proteobacteria, while there is a lower abundance of Actinobacteria, Bacteroidetes, and Firmicutes [115, 116]. Additionally, some species, such as *Stenotrophomonas maltophilia*, *Chryseobacterium*,

Pedobacter, *Stenotrophomonas*, *Variovorax*, and *Pseudomonas stutzeri*, have been associated with the presence of *H. pylori* infection [117].

H. pylori is abundant in the gastritis stage, but as the carcinogenesis cascade progresses other pathogenic microbial strains predominate. Transgenic mice models showed that more severe gastritis and earlier appearance of neoplastic lesions develop in animals with mixed colonization of *H. pylori* and commensal flora, compared to *H. pylori* infection in germ-free animals [118, 119]. Increased abundance of *Achromobacter*, *Citrobacter*, *Lactobacillus*, *Clostridium*, *Rhodococcus*, and *Phyllobacterium* was reported in the GC flora [120]. Similarly, abnormalities of the gastric microbiota were identified in a cohort of GC patients followed by validation in a second cohort. Increased abundance *of Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes* was crucial to the GC occurrence [121]. These are strong indications that gastric microbiota is associated with GC pathogenesis.

Clinical approaches of the role of bacteria other than *H. pylori* have produced diversified results with individual bacterial flora possibly influenced by the different populations studied having different dietary habits. Thus, gastric biopsies from a high-risk GC area were compared with biopsies from an area with a 25-fold lower risk of GC in Colombia. The high-risk region patients showed an increased abundance of *Leptotrichia wadei* and *Veillonella* spp. While *Staphylococcus* spp. was more increased in the low-risk region [122]. Biopsies from GC patients had considerably decreased diversity and overrepresentation of non-*Helicobacter* Proteobacteria compared with patients with chronic gastritis only [123]. *H. pylori*, *Prevotella copri*, and *Bacteroides uniformis* were less prevalent, whereas *Prevotella melaninogenica*, *Streptococcus anginosus*, and *Propionibacterium acnes* were more abundant in the tumor microenvironment [124].

The eradication of *H. pylori* induces considerable changes in the diversity of the gastric microbiome supporting the hypothesis that the presence of *H. pylori* provides various microbiome changes contributing to GC development. An analysis of biopsies taken before and after *H. pylori* eradication demonstrated that *Roseburia* and *Sphingomonas* were reduced in patients with persistent inflammation one year after *H. pylori* eradication. Persistent gastric atrophy and IM one year after *H. pylori* eradication were associated with an abundance of oral bacteria including *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella*, *Rothia*, and *Granulicatella* [125]. A recent study demonstrated that most phyla were similar between successful and failed eradication but the microbial diversity was decreased in the failure group with lower species abundance. *H. pylori* eradication was associated with the presence of *Rhodococcus*, *Lactobacillus*, and *Sphingomonas* [126].

Bacteria other than *H. pylori* have been identified in conditions of hypochloridria with an oncogenic potential due to the increased secretion of *N*-nitroso compounds [127, 128]. Thus, Nitrospirae were found in *H. pylori*-negative patients. Nitrospirae containing nitrite-oxidizing bacteria were present only in the gastric mucosa of all patients with GC but not chronic gastritis [129]. A possible role of *mycobacteria* has also been suggested but not clearly proven. Interestingly, *Mycoplasma hyorhinis* has been shown to activate the β-catenin signaling pathway and promote the motility of GC cells a fact that could influence the metastatic potential of GC [130].

Profound alterations of the gastric microbiota were also reported in children. Lower gastric bacterial diversity and significantly different microbial compositions were demonstrated compared to those without *H. pylori* infection. Decreased abundance of Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Gemmatimonadetes, and Verrucomicrobia were significantly decreased in *H. pylori* infected children. At the genus level, *Achromobacter*, *Devosia*, *Halomonas*, *Mycobacterium*, *Pseudomonas*, *Serratia*, *Sphingopyxis*, and *Stenotrophomonas* were more abundant in the *H. pylori*-negative group [131, 132].

H. pylori infection is associated with alterations not only of the gastric microbiota, but with changes in the gut microbiota as well. They include a decreased abundance of *Parasutterella* and increased levels of *Haemophilus* and *Pseudoflavonifractor*. The *H. pylori* antigen load was negatively correlated with the abundance of *Bacteroides*, *Fusicatenibacter*, *Alistipes*, and *Barnesiella* [133]. The influence of *H. pylori* is direct but in most instances is mediated through drug-based eradication treatments [134].

Other studies have demonstrated additional alterations in the gut microbiota of *H. pylori*-infected patients. The genus *Succinivibrio*, and the families Coriobacteriaceae, Enterococcaceae, and Rikenellaceae were dominant. *Candida glabrata* and other unclassified fungi were also found in abundance. It was suggested that these *H. pylori*-associated changes might impair the integrity of the intestinal barrier and interfere with the development of colorectal carcinoma [135]. Interestingly, gut microbial vitamin B12 biosynthesis was significantly lower in *H. pylori*-positive individuals [136]. A 7 days antibiotic eradication regimen disturbed the oral and colonic microbiota that persisted for up to 4 years [137]. A 14 days of quadruple eradication treatment reduced diversity for 6 weeks post-treatment [138]. Phylum alterations were only transient and lasted for 2–3 months. Transient decrease of Firmicutes, Bacteroidetes, Verrucomicrobia, and Lentisphareae, and an increase in Proteobacteria and Cyanobacteria were observed [138]. Treatment regimens combined with probiotics reduce the negative effects of antibiotic therapy on the gut microbiota [139].

In view of the above evidence several authors have suggested that *H. pylori* sets the stage of a premalignant pathology of AG and IM resulting in *H. pylori* substitution by a cancer-prone microbiota. These later shifts in gastric microbiota composition play an important role in gastric tumorigenesis itself [140–144].

Arguments against *H. pylori* eradication

H. pylori is living with humans over innumerable millennia, and may be a harmless bacterium [145]. It has been suggested that this co-evolution may be beneficial for humans, but this is still debatable [114, 146, 147]. In the previous subsections, we presented the rationale for mass eradication regimes. However, there are several reasons for concern including the increasing antibiotic resistance and the relatively unknown consequences of gut microbiota alteration [148, 149].

The first problem with eradication is the development of antibiotic resistance that varies in different countries. European resistance to clarithromycin is around 20%, to levofloxacin is 11.0–16.3%, and to metronidazole may reach 56% [150] with an increase in these numbers in Southern Europe compared to the North [151]. In the USA, resistance to clarithromycin is around 10% [152]. The numbers for clarithromycin, metronidazole, and levofloxacin in China and South Korea are estimated at 28.9%, 63.8%, and 28.0%, respectively [153, 154]. Particularly alarming is the fact that in children in southeast and southwest China, the resistance rates were 32.8%, 81.7%, and 22.8% in the southeast and 55%, 71%, and 18% in the southwest for the three antibiotics respectively. Double resistance was found in 28.7%, and triple resistance in 9.0% of cases [155, 156]. Equally alarming is a study from Jordan, where 82.7% of patients had not received a prior treatment for *H. pylori* eradication. The resistance was 25.9% for clarithromycin, 50% for metronidazole, and 6.9% for levofloxacin [150]. High resistance to clarithromycin at 23.2% not related to gender or age, was also detected in Northern Greece. Common mutations were A2142G and A2143G [157]. One of the consequences of increasing resistance is the observed reduction of treatment success. It has been suggested therefore, that empiric use of clarithromycin, metronidazole, and levofloxacin triple therapies should be abandoned [158].

A second problem with eradication strategies is the effects on microbiota. As mentioned before, the current guidelines suggest an unconditional eradication based on the "test-and-treat" strategy [68]. However, an alternative attitude has emerged viewing *H. pylori* as a commensal symbiont [159, 160]. Already in 1998, it was proposed that *H. pylori* can be regarded as part of the commensal flora, acquired within the first few years of childhood and retained for a lifetime [159]. In contrast to most other bacteria, *H. pylori* colonization of infants is facilitated by T helper 2 immune response leading to the development of immune tolerance [161] as *H. pylori* is not considered a pathogen by the immune system. This is in concert with the fact that α1,2-fucosylated glycans of the gastric epithelium, which normally protect against pathogens, help the adhesion of *H. pylori* and successful colonization [162]. Early colonization of *H. pylori* can have beneficial effects such as the regulation of the hormone leptin and protection against some diseases [161, 163]. Moreover, *H. pylori* may inversely regulate pro-inflammatory or pro-carcinogenic bacteria as reported in several studies.

Therefore, eradication of *H. pylori* will profoundly change the total microbiota. Indeed, *H. pylori* eradication, apart from the stomach, will additionally modify the intestinal microbiota leading to dysbiosis [164]. Dysbiosis after *H. pylori* eradication may be due to the use of antibiotics or proton pump inhibitors (PPIs) or the loss of *H. pylori* itself [138, 165]. Long-term (≥ 6 months) changes in the gastric microbiota after *H. pylori* eradication have been described. Two studies have shown that eradication led to enrichment of the corpus with the pro-inflammatory *Acinetobacter* and a decrease in microbial diversity of more than 50% of patients with endoscopic follow-up for > 1 year [125, 166]. Importantly, several bacteria in the gastric mucosa such as *Actinomyces*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Rothia*, and *Streptococcus*, originally coming from the oral cavity were related to the precancerous lesions of AG and IM, one year after eradication [125, 167]. As mentioned before, short-term changes including reduction of Actinobacteria and increase of Proteobacteria and Enterobacteriaceae that returned to baseline levels have also been described [114]. Disturbance of microbiota occurs not only with triple antibiotic eradication, but also with the bismuth quadruple therapy that may lead to short-term dysbiosis with an increased abundance of Proteobacteria and decreased abundance of Bacteroidetes and Actinobacteria [168]. Bismuth quadruple eradication was also associated with significant changes in the gut microbiota that did not recover 6 weeks after treatment [138]. It should be noted however that another study reported beneficial effects on gut microbiota, including increased probiotic *Bifidobacterium* and downregulation of drug-resistance mechanisms after *H. pylori* eradication [143]. *Butyricimonas* spp., including *Butyricimonas virosa*, [169] as well as *Bacteroides coprophilus* [170], which are associated with several diseases were enriched in *H. pylori*-positive individuals [138]. Pro-inflammatory *Prevotella copri*, related to rheumatoid arthritis and microscopic colitis as well as *Enterobacter cloacae* and *Klebsiella pneumoniae* usually associated with hospital infections, were also abundant in *H. pylori*-positive individuals [136].

A third reservation for the general eradication of *H. pylori* refers to the increased body weight after eradication. A recent study generally confirmed the incomplete restoration of microbial diversity after one year and noticed a significant increase in body mass index (BMI) [171] in agreement with a previous report [172]. Various mechanisms have been proposed such as the improvement of postprandial dyspepsia [172] alterations in the regulation of leptin and ghrelin [173] and the imbalance between bacterial production of lactate and acetate [174]. So far, the data are contradictory indicating weight gain, weight loss, or the absence of an effect obviously due to the differences in populations, dietary habits, and composition of the intestinal microbiota [175].

However, a direct consequence of these findings is that the wealth of papers reporting on the normal or abnormal gut microbiota should take into account the presence or eradication of *H. pylori*. In contrast, several other beneficial effects are mostly well-documented.

H. pylori and reduced risk of inflammatory bowel disease

The potential protective effect of *H. pylori* in inflammatory bowel disease (IBD) may be related to its influence on the gut microbiota and the modulation of the immune response [176]. The microbiota modulation is supported by an inverse association between *H. pylori* and several pro-inflammatory microbes such as *Fusobacterium varium*, *Rhodococcus*, and *Sphingomonas*, while the activation of colonic mucus production by *H. pylori* via the NLR family pyrin domain containing 3 (NLRP3)/caspase-1/IL-18 axis argues in favor of the immunomodulation effect [177, 178]. An additional possibility was proposed suggesting a non-causal relationship between *H. pylori* and IBD. Individuals with a defective fucosyl transferase 2 (*FUT2*) gene cannot secrete fucosylated glycans in the GI mucosa. They are susceptible to pathogens such as *Escherichia coli*, *Neisseria meningitidis*, and *Candida albicans*. The FUT2 non-secretors are more susceptible to Crohn's disease (CD), ulcerative colitis (UC), and other so-called autoimmune diseases but at the same time, they are protected against *H. pylori* adhesion in the gastric mucosa [162, 179–181]. Patients with UC and CD had decreased FUT2 expression in the colon [182]. The increased susceptibility to IBD was possibly associated to increased production of microbial lysophosphatidylcholine that promotes the secretion of pro-inflammatory cytokines, damaging the tight junctions and the intestinal epithelial barrier [182]. These deleterious effects were reversed by upregulation of FUT2 [183]. However, even this

theory cannot rule out that *H. pylori* is in fact the mediator of the protection offered by fucosylation against IBD modulating either the gut microbiota or the immune system [178].

From the clinical point of view, epidemiological studies revealed that IBD is more prevalent in areas with low prevalence of *H. pylori* infection while several meta-analyses reported a negative correlation between *H. pylori* infection and IBD attributing a protective role to *H. pylori* [184–186]. *H. pylori* infection seems to provide more protection against UC than CD, and in East Asian populations compared to Mediterranean ones [185]. A meta-analysis involving 13,549 patients with IBD and 50,654 controls [187] reported that the prevalence of *H. pylori* infection was 22.8 % in patients with IBD and 36.3% in controls, finding a significant negative association (pooled OR = 0.45). Another meta-analysis also demonstrated a strong negative correlation between *H. pylori* prevalence and IBD. The odds of colonization were 0.36 for CD and 0.54 for UC. Most importantly, *H. pylori* eradication could lead to IBD flares, while patients had a higher probability of relapse after the eradication (OR = 1.41) [188].

H. pylori and esophageal diseases

The absence of *H. pylori*, mostly after eradication, has been linked to some esophageal diseases including gastro-esophageal reflux disease (GERD), Barrett's esophagus, and adenocarcinoma of the gastroesophageal junction [14, 189–191] as the incidences of these diseases have risen in developed countries and are negatively associated with *H. pylori* prevalence [192–195].

Explanations for the protective effect of *H. pylori* include the reduction of acid secretion and the colonization with other organisms. There is a reduced production of acid by the infected stomach and the microbiota of the distal esophagus is probably affected when reflux occurs [145] a situation similar to protracted administration of PPIs [196, 197]. A protective *H. pylori* effect has been also proposed for the new entity of eosinophilic esophagitis, but this conclusion is controversial [198].

From the clinical point of view, an earlier prospective study with endoscopic assessment demonstrated that eradication therapy in duodenal ulcer patients will increase the prevalence of reflux esophagitis compared to those without *H. pylori* eradication. Risk factors were the corpus atrophy and weight gain [199].

It was also reported that *H. pylori* presence can considerably reduce the risk of esophageal adenocarcinoma in Western populations. On the other hand, esophageal squamous cell carcinoma (ESCC) risk was not affected for the combined populations from East and West. However, when populations were separated, there was an association with decreased risk of ESCC in populations in East Asia [200]. This observation is difficult to be attributed only to *H. pylori* eradication as ESCC is related to several dietary and lifestyle factors such as alcohol consumption, cigarette smoking, and hot-temperature food [200, 201]. Different genetic background cannot be excluded as well [202]. A study from Greece, reported an inverse association of *H. pylori* infection with both esophageal adenocarcinoma and Barrett's esophagus, suggesting a protective role of *H. pylori*. On the contrary, no association with ESCC could be established [203]. A cross-sectional study in a large Japanese population found that seropositivity for *H. pylori* was related to a lower rate of long-segment Barrett's esophagus and a higher rate of short-segment Barrett's esophagus [204], findings that are difficult to reconcile. Another study confirmed that the presence of *H. pylori* in the stomach was associated with a significantly decreased risk of Barrett's esophagus, and esophageal adenocarcinoma [205]. The OR for the association between *H. pylori* and Barrett's esophagus after controlling for age and white race was 0.55 with an even higher inverse association (OR = 0.28) among participants with corpus atrophy or anti-secretory drug use more than once per week. Although the authors imply that these factors are the reason for the negative association, it should be noted that *H. pylori* infection is the main reason for corpus atrophy. By contrast, no inverse association was found in patients without these factors [206]. A recent meta-analysis also observed an inverse relationship between *H. pylori* and Barrett's esophagus (OR = 0.70) [207]. However, these inverse associations are still debatable [208], and evidence for positive [195, 203, 209, 210] and negative associations exist [208, 211]. It should be noted however, that in the recent negative study, almost 50% of patients had only 1–2 years follow up and only 15% of them had a maximum follow-up of 5–7 years [211]. A recent meta-analysis found an inverse association between *H. pylori*

infection and erosive gastritis but no association with Barrett esophagus [212]. At present, the most recent recommendations have chosen to ignore the alarming positive studies, which made no impact on the management of the *H. pylori* infection [213].

This attitude was influenced by a recent large retrospective study in the USA that reported no association of *H. pylori* infection or eradication with the development of either esophageal cancer or proximal gastric adenocarcinoma. Despite the large number of patients enrolled, there are substantial drawbacks in the study. Only gender, age, race, and smoking habits were considered as covariates. Critical risk factors such as dietary habits and alcohol use were not included possibly due to the retrospective nature of the study. Moreover, smoking was tested on the yes or no situation without any attempt to categorize patients on the basis of pack/years. More importantly, only 30% of treated patients had a confirmed outcome while almost 70% were categorized as unknown outcomes. Probably these are the explanations for the somewhat curious finding that Asians and native Hawaiians were protected from the future cancers [214].

H. pylori and protection from asthma and allergy

Earlier reports from Europe and the USA have demonstrated a significant inverse association between asthma and *H. pylori* infection [146, 147, 215–218]. Protection from childhood-onset asthma, hay fever, and cutaneous allergies by the presence of *H. pylori* infection has been confirmed by several reports [219–223] including a recent report from Greece [224] and a meta-analysis of 24 reports where it was shown that *H. pylori* infection, especially CagA-positive infection, is inversely associated with the risk of asthma [225]. Therefore, there is considerable evidence to support the hypothesis that the rise in asthma prevalence may be related to the reduced prevalence of *H. pylori* and the protective immunological functions elicited by its presence [145, 223, 226]. Murine studies reported that *H. pylori* protects from allergic asthma by modulating effector T-cells and T regulatory cells (Tregs) and by limiting dendritic cell (DC) function [226–229].

Additional rodent experiments showed that mothers infected by *H. pylori* during pregnancy initiate a tolerogenic immunity response to their offsprings that mitigated the development of allergic diseases later in life [230]. In a murine study of mice sensitized with house dust mite, it was shown that extracts of *H. pylori* were an effective treatment to reduce mucus production and features of inflammation when re-challenged with dust several months after rest [231]. In a similar model, a very recent report demonstrated that treatment with *H. pylori*-derived VacA reduced several asthma indicators such as inflammation and goblet cell metaplasia. An induction of tolerogenic DCs and regulatory T cells were observed after VacA administration. Depletion of regulatory T cells, reversed the CagA suppression of allergic airway disease [232, 233]. VacA targets DCs and macrophages of the gastric lamina propria [234] promoting the secretion of anti-inflammatory molecules such as IL-10 and transforming growth factor-β, and modulating the development of Tregs [234]. Moreover, naive human DCs incubated with VacA increased the expression of programmed death-ligand 1 (PD-L1), a molecule that is strongly associated with amelioration of T cell reactions [235, 236]. In addition, VacA also initiated the expression of immunoglobulin-like transcript 3 (ILT3), an inhibitory receptor that is found in tolerogenic DCs [237].

Interestingly, the effect of *H. pylori* may be dependent on ethnicity as demonstrated in a multiethnic study of children. Children of European ancestry colonized with CagA-negative *H. pylor*i had an increased prevalence of asthma in contrast to children of non-European origin. In addition, only positive children with *H. pylori*-negative mothers had an increased risk of asthma suggesting again that, in agreement with the previously mentioned animal data, infection of the mother may protect the *H. pylori*-positive children [238]. In a case-control study, abdominal obesity and *H. pylori* infection were associated with reduced risk of asthma and allergy. *H. pylori* infection was associated with a considerable reduction odd of asthma and allergic diseases in individuals with abdominal obesity [219]. This is in concert with the change in BMI after eradication [173]. A significant increase in BMI and body weight after eradication of *H. pylori* has been reported which possibly due to the restoration of ghrelin secretion and the relief of dyspepsia, as mentioned before [171, 239, 240].

Negative studies have also been published [241]. However, they included only adults [242] and/or a specific Hispanic/Latino population of 18–74 years old [243]. In the last recent cross-sectional the diagnosis of asthma was only based on self-reported information, while the significant co-variate of smoking was reported as current, past, and never smokers without further quantification according to pack/years of smoking.

Despite these negative reports, the overwhelming evidence supports the protective role of *H. pylori* infection in asthma and other allergic diseases.

Coeliac disease

Coeliac disease affects approximately 0.5–1% of the global population. Increasing evidence of *H. pylori* involvement has been proposed [244] based on a previous large meta-analysis of 25 studies and more than 140,000 participants. The infection rate of *H. pylori* infection of celiac disease patients was almost 50% lower compared to controls with an OR of 0.57 [245].

Other putative protective effects

H. pylori infection was also proposed to protect from pathogens that cause diarrhea, but this observation is not consistent and may be associated with recent changes in other factors [246, 247]. Moreover, this protection may be related to the improvement of sanitation in the industrialized West, rather than to *H. pylori* [145]. Individuals infected by *H. pylori* also show a negative association with tuberculosis. More plausible is the reported reduction of latent tuberculosis re-activation of individuals with *H. pylori* infection in West Africa [145]. It was proposed that *H. pylori* infection may interfere with T-cell signaling pathways that enhance the innate response of the host and reduce the risk of active tuberculosis [145, 248].

Other reasons for abandoning the "test-and-treat" suggestion

A well-known paradox in the relationship between *H. pylori* and GC, is the low incidence of GC in Africa, Asia, and Latin America associated with a high prevalence of *H. pylori* infection even with high virulence strains. This is called the African [249] or Asian/Indian enigma [250]. The very existence of this paradox has been disputed [251], but the genetics of the host population, their dietary habits, smoking, alcohol consumption, and co-infection with parasites should be examined as they may initiate the protective Th2 immune response [249, 250]. The expected GC incidence is 5.7 in African countries, 7.0 in Asia and Oceania, 16.0 in America, and 26.0 in Europe, considering the alcohol and tobacco availability and the consumption of fruit and vegetables. The interaction between *H. pylori* and cigarette or alcohol consumption and dietary habits may explain the so-called African and Asian enigmas [252]. Dietary differences were also proposed to explain a similar enigma in Chile. They studied two areas with similar prevalence of *H. pylori* colonization and similar prevalence of VacA and CagA factors but with different GC prevalence. Chilly consumption was much higher in the high GC incidence area and daily non-green vegetable consumption was more common in the low incidence area [253].

An additional explanation for the enigmas was recently proposed linking them with the co-evolution of *H. pylori* and humans. It was demonstrated that the African human ancestry adapted well to the co-evolution with *H. pylori*, while the European ancestors failed to do so. The Asian ancestry was closer to the African adaptation [254]. Certainly, this cannot be the explanation for the Cretan enigma where in Crete (Greece) a dissociation between GC rates and *H. pylori* infection was reported. In Crete, there is a prevalence of *H. pylori* colonization of over 70% for individuals over 50 years of age associated with the lowest mortality from GC among participants from 17 populations in 13 countries [255]. And this is not due to a low prevalence of CagA, as its prevalence is high in the Greek population [256].

Is QoL improved?

The last point that should be examined is the unequivocal evidence that generalized eradication of *H. pylori* improves the QoL. Several different questionnaires have been used to assess QoL in *H. pylori* associated diseases before and after eradication. The results have been controversial. Eradication of *H. pylori* was reported to either improve [257] or have no effect on QoL. A large randomized controlled study of QoL

using a validated dyspepsia reported no effect on QoL following eradication [258], a finding confirmed by a later smaller study [259]. By contrast, reports from Hungary, Croatia, and Rwanda showed improved QoL [260–262]. However, a study also from Rwanda reported reduced quality [263]. No conclusive comments can therefore be made.

Is there a viable alternative?

The Mediterranean diet (MD) attracted interest after extensive studies indicated that mortality from cardiovascular disease in the Mediterranean countries was lower than that in northern Europe [264, 265]. This advantage has been reduced but not lost over the years [266] possibly due to changes in dietary habits.

It is now fairly established that MD can protect from GC. Earlier studies confirmed the beneficial effect of MD in GC prevention. A Greek case-control study showed that a low consumption of fruit and vegetables was associated with an increased risk of GC [267]. Similar findings were reported from Italy [268, 269]. Although no specific information on infection by *H. pylori* was available in the Italian studies, it is probable that both cases and controls were equally infected as this Italian population has a 45% prevalence of *H. pylori* colonization [270, 271]. Studies from Uruguay and Canada also found a significant reduction of GC after consumption of fruit and vegetables [272, 273]. Furthermore, a meta-analysis of dietary patterns found a two-fold increased GC risk between a diet rich in fruit and vegetables and a diet rich in meat and fats [274]. The protective effect of the MD in risk reduction of GC were confirmed by large more recent studies. Adherence to the MD considerably reduced the risk of GC in parallel with the degree of MD adherence. Importantly, risk estimates were consistent when co-variates such as smoking, BMI, and family history of GC were taken into account [275]. In the large Netherlands cohort study, higher MD adherence was associated with reduced risks of ESCC carcinoma and adenocarcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma. It seems though that the decreased ESCC carcinoma risk might be limited to men [276]. A large recent meta-analysis based on 117 studies with more than 3,000,000 participants conclusively showed that the highest adherence to MD was inversely associated with cancer mortality and specifically with GC mortality [277]. Eleven studies were included in another meta-analysis and revealed that adherence to the MD was inversely associated with GC risk (OR =0.43) [278]. In a large case-control study from Spain, an adherence to MD was protected from GC. Risk reduction was 48–68% for high adherence and 16–57% for medium adherence to MD and applied to both gastric cardia and non-cardia GC. Histology confirmed a significant protective effect for IM between 41% to 72% for high adherence *versus* low adherence. However, in the diffuse type of cancer, only one of the five indices used to verify adherence to MD was associated with a protective effect [279]. These findings were confirmed by a very recent report from Afghanistan a country with a very high prevalence rate of *H. pylori* infection. A greater adherence to MD was associated with a lower odd of GC [280]. Interestingly, the potential benefits for the health care system are savings of 55 billion dollars (range 41.8 billion to 68.2 billion) annually in the USA alone [281, 282].

In addition to the protective effects of MD, there are other factors that interfere with an increase of GC prevalence. Tobacco smoking and alcohol consumption are prevalent among them. Thus, a study on GC mortality demonstrated a decrease in GC incidence rates more evident in males. This may be due to the fact that smoking consistently decreased in men rather than in women in most countries [283]. Smoking was linked to all precancerous lesions of the stomach such as AG, IM, and dysplasia. The risks were dose-dependent [284].

The important associations between risks of GC and alcohol consumption, use of salt-preserved foods, and increased body weight were reported in a meta-analysis of 49 studies. Heavy (> 42 g/day) alcohol consumption, salted fish, and increased BMI were significantly associated with an increased GC risk. An inverse association was associated with a healthy lifestyle index with a risk reduction of approximately 40% [285]. A meta-analysis of 38 case-control studies confirmed the strong positive association between high salt intake and GC [286]. The increased positive association between excess body weight and the risk of GC seems to be more important in women than men and in non-Asian compared to Asian populations [287]. A recent review has corroborated all the above findings [288].

In view of the problems of antibiotics used in *H. pylori* eradication, a promising review was recently published reporting the results of traditional Chinese medications on *H. pylori*-associated gastritis. Significant therapeutic benefits were demonstrated that may justify a more detailed investigation on this subject [289].

However, the best choice in the elimination efforts of *H. pylori* is the development of vaccines. A complex oral vaccine was tested in a mouse model of *H. pylori* infection for immunogenicity and therapeutic efficacy. A reduction of colonization was observed in connection with an induction of Th1/Th17 immune responses that may overcome the immune evasion caused by *H. pylori* [290]. An intranasal vaccine has also been tested with promising results [291].

Additional problems

Are all metaplasias similar?

IM is classified into three distinctive types: the small intestinal phenotype, the complete type, or type I, where cells secrete sialomucins and the incomplete types, or types II and III, where goblet cells secrete neutral and acid sialomucins in type II and sulfomucins in type III. It has been reported that type III IM has an increased risk of malignant transformation compared to types I and II [292, 293]. Specifically, in type I, the expression of the mucin MUC2 is dominant, while mucins MUC1, MUC5AC, and MUC6 are decreased. Instead, in type II/III, there is co-expression of MUC2 with the other mucins [294, 295]. Moreover, in IM, the presence of a metaplastic mucous cell lineage called spasmolytic polypeptide-expressing metaplasia (SPEM) is very important. It strongly expresses trefoil factor 2 (TFF2), formerly known as spasmolytic polypeptide. The name pseudopyloric metaplasia was used in the past to indicate the presence of SPEM. SPEM is more closely associated with the development of GC compared with IM [296]. Interestingly, IM is usually spotty or multifocal, but SPEM is diffuse throughout the body and corpus of the stomach in patients that will develop GC [293]. The connection between IM and SPEM and the relationship between SPEM and GC requires further investigation [297]. SPEM appearance is probably due to acute injury or inflammation of the gastric mucosa and the overproduction of IL-33 by macrophages. Gastric glands with lineage mixture such as incomplete IM intermixed with SPEM metaplasia are at particular risk for progression to dysplasia and cancer. The connection of *H. pylori* with SPEM malignant evolution is under investigation [298–300].

An additional problem with the interpretation of studies corelating *H. pylori* with the GC is the role of pathological reports. Pathologists' agreement is very poor in the evaluation and categorization of atrophy with kappa coefficients varying from 0.08 and 0.29 [301, 302]. In a more recent study, the interobserver agreement was very good for IM ($\kappa = 0.81$), not so good for dysplasia ($\kappa = 0.42$), and poor for AG ($\kappa < 0$) [303].

The extent of the problem of GC

It is a common practice in all studies on *H. pylori* and GC to declare their connection based on epidemiological and experimental research. The exact quantification of this relationship is not always clear. A large study from a cohort in the Netherlands reported that 24% of patients were diagnosed with AG, 67% with IM, 8% with mild-to-moderate dysplasia, and only 0.6% with severe dysplasia. A re-evaluation after 5 years showed that the annual incidence of GC was 0.1% for patients with AG, 0.25% for IM, 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia. Risk factors for GC development were severe dysplasia, old age, and male gender [304]. A recent study endoscopically assessed the evolution of the Correa's cascade after *H. pylori* eradication. Correa's steps III–V, but not I–II, were at risk of GC after *H. pylori* eradication. Age, OLGA stages I, and OLGIM stages were also independent factors of GC development. Eradication of *H. pylori* decreased Correa's step progression (relative risk = 0.66), but it did not regress OLGA and OLGIM [305]. Moreover, as was already mentioned, the results between the prevalence of *H. pylori* infection and the actual appearance of GC are not linear. Even European countries have high *H. pylori* colonization and low GC [252].

Problems with eradication studies

The vast majority of the trials are retrospective. Most of them do not take into account the three fundamental risk factors in the development of GC namely, smoking, alcohol consumption, and salted food consumption. Even those that use it as a co-variate either smoking or alcohol do it in a crude way. Smoking is not categorized according to pack/years, and alcohol is not reported according to various levels of daily or weekly consumption.

Meta-analysis is considered the holy grail of evidence-based medicine considered superior to any other form of study. However, meta-analyses have an inherent problem. They end up analyzing a few studies after rejecting hundreds of others for various reasons. For example, in a systematic meta-analysis, the authors initially identified 8,061 papers and finally included only 24 [61]. Another study started with 17,438 reports screened and finally included only 149 [13].

An additional problem with this type of report is the fact that conclusions may have a different approach. As an example, two systematic studies conclude that there is a strong relationship between *H. pylori* infection and GC prevalence. However, in the majority of included studies, the statistical significance is doubtful as the 95% confidence intervals in the forest plot cross the significance line [61, 306].

As a consequence of the unresolved problems of heterogeneity, almost all studies manipulate statistics as they try to incorporate as many confounding factors as possible. This is a perfectly accepted practice, but may end up with precarious results. Two decades ago, a very illuminating observation was reported in the field of hepatology, but it is relevant in other fields as well. The authors investigated the 20-year survival of the scientific truth according to the type of publication. They found that there was no difference between randomized controlled trials and nonrandomized studies. Unexpectedly, the lowest truth survival was observed in the meta-analyses and the conclusions founded on good methodology remained true for similar periods as those based on poor methodology. This rather unorthodox view should be seriously taken into consideration when assessing papers heavily based on statistical adjustments [307, 308].

Finally, the multi-national studies of mixed populations should be scrutinized as the evolution of *H. pylori* infection is heavily dependent on geographical and genetic criteria as suggested in a real-world report from Japan [309].

Reinfection is another problem in this group of patients

Most studies on eradication results, including studies on the relevant costs, do not evaluate the effects of reinfections. Recent studies reported on the reinfection rates of *H. pylori*. In a cohort from South Korea of over 10,000 eradicated individuals, reinfection of *H. pylori* was calculated to be 3.06% per person-year [310]. In a prospective, observational study in China the annual reinfection rate was 1.5% [311]. The oral cavity is considered as an extra-gastric source of *H. pylori*, because of the presence of *H. pylori* DNA in certain areas of the oral cavity. Bacteria from the oral cavity may therefore be responsible for eradication failure, and reinfection [312]. The annual reinfection rate after successful eradication is low (< 2%) in the developed countries, where eradication may not be the first health priority, but is considerably higher (5–10%) in developing countries and children [6, 171]. A meta-analysis showed that a strategy of family-based *H. pylori* screening and treatment may be more effective than a single-patient approach [313].

Recommendations again

Despite the previously described problems and reservations, it is somewhat odd that most recent recommendations still support that eradication therapy should be offered to all individuals infected with *H. pylori* on the test-and-treat strategy [6]. Some reservations are related to substantial health costs and risks of the massive use of antibiotics. Although the generalized elimination is still on, the identification of population subsets with a higher-than-average risk of GC is also considered [213].

The American College of Gastroenterology (ACG) recommends extensive testing, including all peptic ulcer patients, patients with uninvestigated dyspepsia under the age of 60, patients on long-term non-steroidal, anti-inflammatory drugs, and patients with unexplained iron deficiency anemia [69]. The Taipei

consensus [6] and the Houston conference [96] support similar recommendations with the inclusion of first-generation immigrants from high prevalence areas or populations with a high incidence of GC [314]. Gastroenterologists from China in their consensus report also recommend a population test-and-treat policy adding that eradication of *H. pylori* is a cost-effective measure to prevent cancer in high-risk areas despite the fact that the evidence they refer to is rather obsolete and a recent robust study with proof of cost-effectiveness is lacking. They also suggest that no adverse consequences should be expected [95]. The last notion is at least very doubtful. The prevalence of antibiotic resistance to *H. pylori* is rising in Asia [315]. The primary resistance in Asia is approximately 17% for clarithromycin, 44% for metronidazole, and 18% for levofloxacin and rising [152] as mentioned before.

Adding a one to two-week course of *H. pylori* eradication therapy is suggested in the above recommendations to treat and prevent recurrence of peptic ulceration. However, this is not supported by current evidence. There is no evidence supporting the idea that *H. pylori* eradication is an effective treatment for people with gastric ulcer or that it is more effective in the prevention of recurrence of duodenal ulcer compared to traditional drugs such as PPIs. When observing the forest plots of a Cochrane systemic review this is evident and only a slight advantage is present in duodenal ulcer [316]. This is further supported by a recent review indicating that *H. pylori* is not the main cause of peptic ulceration so empirical eradication should not be used in these patients [27]. Moreover, the old practice of biopsy all gastric ulcers to check for malignancy and to repeat endoscopy after PPI treatment to check for ulcer healing is still imperative [317]. It is now evident that there are several causes of peptic ulceration in addition to *H. pylori* infection [318]. Peptic ulcers are detected without an obvious etiological agent, so they are called true idiopathic peptic ulcers and account for approximately 10% of the total [319]. Therefore, the traditional practice of empirical eradication in patients with duodenal ulcers is no longer justified.

Another important problem with the current recommendations is the age when test-and-treat should start. It is rationale that treatment should be given before dysplasia has been reached, but no reliable marker exists to detect premalignancy on time. Serum pepsinogen assay has been proposed as a screening test but a mass scale implementation may not be feasible [320]. Extensive validation studies are also required. On the other hand, the prevalence of *H. pylori* infection has significantly reduced in recent years, and screening for the very young is probably not cost-effective. The suitable age for screening therefore is still open to debate [321].

Who really needs eradication?

It is generally accepted that no disease can be eradicated with methods based on treatment regimes. Only yaws, was eliminated because of its presence in a localized area and use of inexpensive drugs [322]. Even significant reductions of harmful consequences, such as GC after *H. pylori* eradication, are very hard to achieve. Effective affordable vaccines are indispensable. However, vaccine development for *H. pylori* is not, a priority of the pharmaceutical industry for the time being [323].

In view of the evidence presented before, we believe that the population-based test-and-treat policies of eradication in every individual tested positive is not useful as *H. pylori* is a harmless commensal in the vast majority of cases [160]. Moreover, eradication may have detrimental consequences in several groups of patients [191]. On the contrary, the current attitude in *H. pylori* eradication should be reserved for specific groups of patients. This is the case for first-degree relatives of patients with GC or even in family members living in the same household as the index patient in world regions with high GC incidence [324]. This approach is proposed even from the supporters of the global eradication policies [213]. This is also the case in extensive AG or the type III IM with SPEM presence, diagnosed after gastroscopy performed for other reasons. These patients deserve surveillance endoscopy as well. Needless to say, classification of gastritis and metaplasia according to OLGA and OLGIM systems should be encouraged [27]. Additionally, *H. pylori* should be eradicated after endoscopic resection of early GC to prevent future metachronous lesions [64]. The rare cases of patients with MALT lymphomas [325] and individuals at high hereditary risk of GC should also be eradicated [65].

Patients with diseases negatively associated with *H. pylori* eradication should be treated only if they belong to the previously described groups [326]. A special group is the old people with multiple eradication failures. The American Gastroenterological Association recommends that after several failures of eradication, the potential risks of adverse effects should be judged against the benefits of eradication. [327]. This is because these patients may easily develop severe *Clostridioides difficile*-associated diarrhea and colitis [328] and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca* [329].

An interesting subpopulation that may warrant a priori eradication of *H. pylori* has emerged after the introduction of check point inhibitors in the immunotherapy of various cancers. A worse survival has been reported after immunotherapy in *H. pylori*-positive patients with melanoma, non-small-cell lung cancer and advanced GC [330–332].

Conclusions

Evidence suggests that the population-based test-and-treat policies of eradication in every individual tested positive may be not useful and eradication may have detrimental consequences in several groups of patients. Eradication should be reserved for specific groups of patients such as the first-degree relatives of patients with GC and family members living in the same household as the index patient in geographical areas with high GC incidence. Eradication should be performed in cases of extensive AG or the type III IM with SPEM presence. Classification of gastritis and metaplasia according to OLGA and OLGIM systems should be encouraged. Additionally, *H. pylori* should be eradicated after endoscopic resection of early GC and in the rare cases of patients with MALT lymphomas and individuals at high hereditary risk of GC. Old people with multiple eradication failures should be eradicated only when the potential benefits outweigh the potential risks. A priori eradication of *H. pylori* may be indicated in patients treated with check point inhibitors in the immunotherapy for various cancers.

These comments leave only one question to be answered. In the end, should we establish population-based extensive eradication programs at least in countries with very high prevalence of *H. pylori* colonization? The African-Asian-Greek paradox strongly argues against a generalized recommendation. Most importantly, we believe that there is now overwhelming evidence that adoption of the Mediterranean type of diets, and promotion of policies against alcohol, smoking, and obesity will obtain equal if not much better results with drug treatments of *H. pylori*. Several additional diseases, such as cardio-vascular disease and steatotic liver disease, will be benefited in parallel with GC. It should also be stressed that endoscopy and detailed histologic examination should be the basis for any treatment decision.

Abbreviations

AG: atrophic gastritis

ARF: ADP-ribosylation factor

ATGs: autophagy related genes

BMI: body mass index

CagA: cytotoxin-associated gene A

CD: Crohn's disease

DC: dendritic cell

ESCC: esophageal squamous cell carcinoma

FUT2: fucosyl transferase 2

GC: gastric cancer

H. pylori: *Helicobacter pylori*

IBD: inflammatory bowel disease

ICER: incremental cost effectiveness

IL-8: interleukin-8

IM: intestinal metaplasia

MALT: mucosa-associated lymphoid tissue

MD: Mediterranean diet

OLGA: operative link for gastritis assessment

OLGIM: operative link for gastric intestinal metaplasia assessment

OMVs: outer membrane vesicles

OR: odds ratio

PAMPs: pathogen associated molecular patterns

PPIs: proton pump inhibitors

QALY: quality-adjusted life year

QoL: quality of life

SPEM: spasmolytic polypeptide-expressing metaplasia

UC: ulcerative colitis

VacA: vacuolating cytotoxin A

Declarations

Author contributions

EK: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. IT: Writing—original draft, Writing—review & editing. AV: Writing—review & editing. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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