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Helicobacter pylori infection

Peter Malfertheiner[1,2,✉], **M. Constanza Camargo**[3], **Emad El-Omar**[4], **Jyh-Ming Liou**[5], **Richard Peek**[6], **Christian Schulz**[1,7], **Stella I. Smith**[8], **Sebastian Suerbaum**[7,9,10]

[1]Medical Department II, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany.

[2]Medical Department Klinik of Gastroenterology, Hepatology and Infectiology, Otto-von-Guericke Universität, Magdeburg, Germany.

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA.

[4]Microbiome Research Centre, St George & Sutherland Clinical Campuses, School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Sydney, New South Wales, Australia.

[5]Department of Internal Medicine, National Taiwan University Cancer Center, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan.

[6]Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA.

[7]DZIF Deutsches Zentrum für Infektionsforschung, Partner Site Munich, Munich, Germany.

[8]Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Yaba, Lagos, Nigeria.

[9]Max von Pettenkofer Institute, Faculty of Medicine, Ludwig-Maximilians-Universität, Munich, Germany.

[10]National Reference Center for Helicobacter pylori, Munich, Germany.

Abstract

Helicobacter pylori infection causes chronic gastritis, which can progress to severe gastroduodenal pathologies, including peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. *H. pylori* is usually transmitted in childhood and persists for life if untreated. The infection affects around half of the population in the world but prevalence varies according to location and sanitation standards. *H. pylori* has unique properties to colonize gastric

✉ peter.malfertheiner@med.ovgu.de .

Author contributions

Introduction (P.M.); Epidemiology (M.C.C., J.-M.L. and S.S.); Mechanisms/pathophysiology (S.S., E.E.-O. and S.S.); Diagnosis, screening and prevention (M.C.C., R.P., C.S. and S.I.S.); Management (P.M., E.E.-O. and J.-M.L.); Quality of life (M.C.C., R.P. and S.I.S.); Outlook (P.M. and J.-M.L.); Overview of the Primer (P.M.).

Competing interests

P.M. has consulted for Aboca, Bayer Healthcare, Cinclus, Imevax, Menarini Foundation and Phatom. P.M. has received honoraria for lectures from Allergosan, Biohit, Biocodex and Malesci. S.I.S. has received scientific support from Richen. C.S. has received speaker fees from Imevax, Falk Foundation and Lilly. S.S. is listed as an inventor on a patent application related to the use of bacterial motility inhibitors as potential treatment for *Helicobacter pylori* infection.

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epithelium in an acidic environment. The pathophysiology of *H. pylori* infection is dependent on complex bacterial virulence mechanisms and their interaction with the host immune system and environmental factors, resulting in distinct gastritis phenotypes that determine possible progression to different gastroduodenal pathologies. The causative role of *H. pylori* infection in gastric cancer development presents the opportunity for preventive screen-and-treat strategies. Invasive, endoscopy-based and non-invasive methods, including breath, stool and serological tests, are used in the diagnosis of *H. pylori* infection. Their use depends on the specific individual patient history and local availability. *H. pylori* treatment consists of a strong acid suppressant in various combinations with antibiotics and/or bismuth. The dramatic increase in resistance to key antibiotics used in *H. pylori* eradication demands antibiotic susceptibility testing, surveillance of resistance and antibiotic stewardship.

Introduction

Helicobacter pylori is the most frequent cause of chronic gastritis and variably leads to severe gastroduodenal pathologies in some patients, including gastric and duodenal peptic ulcer disease (PUD), gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[1–3]. The diverse pathologies attributed to *H. pylori* infection are caused by complex interactions of bacterial virulence, host genetics and environmental factors[4,5], which result in different phenotypes of chronic gastritis (Table 1). These phenotypes are defined as antral-predominant, corpus-predominant gastritis or pangastritis according to the highest gastritis severity within gastric anatomical compartments.

The milestone discovery of *H. pylori* invalidated the dogmatic assumption of the acidic stomach as a sterile organ. This finding required a fundamental revision of gastric pathophysiology and gastroduodenal pathologies. Although spiral microorganisms in the stomach had been reported[6], it was not until 1982 that Warren and Marshall identified a bacterial infection as the cause of chronic gastritis and succeeded in isolating the responsible microorganism[7] (Fig. 1). The proof of concept that *H. pylori* infection causes gastritis was obtained by voluntary self-experiments with ingestion of a bacterial broth and cure of gastritis following *H. pylori* eradication (that is, fulfilment of the Koch's postulates)[8,9]. The Koch's postulates requires proof of causality for a pathogen to induce disease and cure of disease when the causal agent is removed — this finding was eventually confirmed in clinical trials[10]. The bacterium originally referred to as *Campylobacter pylori* (*C. pyloridis*) became reclassified as *H. pylori* in 1989 (ref. 11). Peptic ulcer, considered an acid-driven disease in the traditional pathophysiological concept, became an infection-driven disease[12–14]. The standard therapy with long-term acid suppression became short-term *H. pylori* eradication therapy[14]. For the discovery that eventually led to the permanent cure of peptic ulcers by *H. pylori* eradication, Marshall and Warren were awarded the Nobel prize in Physiology or Medicine in 2005 (ref. 15). To this day, continuous scientific progress and new clinical developments have led to frequent modifications and updates to the clinical management of *H. pylori*[10].

H. pylori infects nearly half of the population in the world, with strong differences between geographical areas but with consistent trends towards a decreasing incidence[16]. Around 80%

of individuals with *H. pylori* infection remain asymptomatic, but gastritis develops in all individuals with the infection, with unpredictable and potentially severe individual outcomes as well as high morbidity and mortality[17,18].

This Primer provides an update on current epidemiological trends of *H. pylori* infection, key aspects of its pathogenicity and its role in gastroduodenal pathologies. An important focus is also on gastric cancer prevention by *H. pylori* eradication. The diagnostic and therapeutic management of *H. pylori* infection is discussed according to current international guidelines. The dramatic increase in antibiotic resistance requires special measures, including the incorporation of new molecular methods for antibiotic susceptibility testing, the adaptation of individual treatment regimens and the implementation of antibiotic stewardship.

Epidemiology

H. pylori infection

Once individuals acquire *H. pylori* infection, the pathogen usually persists throughout their lifetime[2]. However, spontaneous clearance was reported in 9 of 58 (15.5%) children during the 20 years of follow-up of a retrospective cohort study from 2002 (ref. 19). Clearance of *H. pylori* does often occur in patients with advanced atrophic gastritis[20]. The global prevalence of *H. pylori* infection in adults has declined from 50–55% to 43% during 2014–2020 (refs. 16,17), mostly attributed to improvement of socioeconomic status, living standards and hygiene conditions[16,21–23]. The increased use of antibiotics, including eradication therapies, in individuals with the infection might be a further contributor.

Prevalence varies substantially with age, ethnicity, associated diseases, geographic regions, socioeconomic status and hygiene conditions[16,21]. For young age groups, the 2002 study showed that most newly acquired *H. pylori* infections occurred before the age of 10 years[19]. The overall crude incidence rate was 1.4% per year, ranging from 2.1% at 4–5 years, 1.5% at age 7–9 years, to 0.3% at 21–23 years of age[19]. During 2014–2020, the prevalence of infection in children and adults was higher in low-income and middle-income countries, including in Africa, the Eastern Mediterranean, Russia, and Middle America and South America, than in high-income countries but was reduced in Western Pacific regions[17] (Fig. 2). The prevalence of infection is higher in adults than in children. It is also higher in rural developing areas than in urban developed regions[2]. Prevalence of *H. pylori* infection in children has been decreasing owing to improvements in socioeconomic status and hygiene conditions; however, the global prevalence in children remained as high as 34% during 2014–2020 (refs. 17,24). The higher prevalence in older individuals compared with children is explained by most (90%) of *H. pylori* infections being acquired in childhood and persisting throughout life rather than by a higher risk of infection at older age.

Some studies suggest increased susceptibilities to *H. pylori* infection in certain populations based on genetics and ethnicity; however, food sharing and housing habits may also have a role[22–24]. For example, in the Sumatra islands of Indonesia, the prevalence of *H. pylori* infection is very low in the Malay and Java populations, but is high in Batak populations, indicating that genetic factors may contribute to differential host susceptibility[25]. Gene and genome-wide association studies have identified that polymorphisms in IL-1B, Toll-

like receptor 1 (TLR1) locus and the FCGR2A locus are associated with *H. pylori* seroprevalence[26,27]. However, a 2022 study has cast doubt on a role of the TLR1/6/10 locus in *H. pylori* seroprevalence[28], and further studies are needed[29].

Faecal–oral and oral–oral routes are considered the most likely routes of transmission[30,31]. Contaminated water may be a source of infection in developing countries[32]. *H. pylori* can be cultivated from the vomitus, stool and saliva of individuals with infection, indicating the potential transmissibility via these routes[33]. However, future studies about transmission pathways and their relative importance are urgently needed.

Person-to-person transmission within families, especially from mothers and siblings with the infection, is common in developing countries[34]. Genotyping studies have shown that strain concordance was detected in 10 of 18 (56%) mother–offspring and in 0 of 17 father–offspring relations[35]. Concordant strains in siblings were detected in 29 of 36 (81%) families[35]. Nevertheless, transmission within couples or spouses remains controversial[35–37]. In two studies, the ribopatterns of *H. pylori* strains were similar in 8 of 18 (44%) and 5 of 23 (22%) couples with *H. pylori* infection[35,36]. However, another study showed that, although restriction fragment length polymorphism patterns were similar in 5 of 13 couples, further restriction fragment length polymorphism using restriction endonucleases revealed distinct patterns in these 5 couples, indicating that transmission between spouses is infrequent[37]. Due to the extremely high genetic diversity of *H. pylori*, even short nucleotide sequences can be highly informative about transmission pathways and the direction of transmission between two individuals. Seven-gene multilocus sequence typing[38] and, more recently, whole-genome sequence analysis[39] have enabled the reconstruction of the spread of *H. pylori* in families and have great potential to answer open questions in *H. pylori* epidemiology.

The annual reinfection or recrudescence rate after successful eradication is low (<2%) in adults in developed countries but is higher (5–10%) in adults in developing countries and in children[17,40]. Some randomized trials showed that a strategy of family-based *H. pylori* screening and treatment can reduce the recurrence rate more than a single-patient approach[41]. Further well-designed, large-scale randomized trials are warranted to validate whether family-based screening and eradication may reduce the transmission of *H. pylori* within families.

H. pylori infection-related diseases

H. pylori infection is an important causal factor of gastric cancer, duodenal ulcer and gastric ulcer[42].

Peptic ulcer disease.—Lifetime prevalence of PUD in individuals with *H. pylori* infection is estimated at around 10%[14,43,44]. After 10 years, >11% of individuals with the infection develop PUD compared with 1% of individuals without the infection[45]. In a prospective study, the lifetime risk of developing duodenal ulcer and gastric ulcer was respectively increased by 18.4-fold and 2.9-fold in individuals with infection with *cagA*-positive *H. pylori* strains[46].

Since the 2000s, the global prevalence of PUD is declining[47–50] in parallel with a decreasing prevalence of *H. pylori* infection[16] for various reasons[47,51–54]. The epidemiological trend indicates an increasing role of NSAIDs, including acetylsalicylic acid, which independently increase the risk of gastroduodenal ulcer and ulcer bleeding[44,53]. Of note, the risk of PUD when using these drugs is further increased in the presence of *H. pylori* infection[55,56].

Despite changing trends in PUD worldwide, *H. pylori* remains the most prevalent cause of PUD. A study from Denmark showed an odds ratio of 4.3 (95% CI 2.2–8.3) for the association between *H. pylori* infection and PUD[57]. In a meta-analysis including endoscopic surveys and national screening programmes in unselected population samples from Europe and China, the pooled prevalence of PUD was 6.8% and PUD was associated with *H. pylori* infection in 91% of cases[58]. Around 3,000,000 diagnoses of PUD per year are estimated to relate to *H. pylori* infections and ~90% of patients with duodenal ulcers and 70–90% of patients with gastric ulcers have *H. pylori* infection with variation according to geographical areas[52,53,58–60].

Gastric cancer.—Around 90% of gastric cancer cases can be attributed to *H. pylori* infection[61]. In 2018, 812,000 gastric cancers, including non-Hodgkin lymphoma of gastric location, were recorded, accounting for ~37% of all cancers driven by a chronic infection, which makes *H. pylori* the most frequent carcinogenic pathogen[62]. Gastric cancer incidence and mortality differ significantly between regions, with the highest rates in Asia and Eastern Europe. The lifetime risk of gastric cancer is 1–5% in individuals with *H. pylori* infection, depending on ethnicity and environmental factors[2,17,63]. Some populations are at an increased risk of gastric cancer following *H. pylori* infection, probably due to genetic factors, housing situation and dietary habits, for example, increased consumption of salted or pickled foods in East Asian populations. In addition, substantially higher gastric cancer incidence is found in indigenous populations worldwide[64] and in ethnic groups in the USA, including Asian Americans[65]. Socioeconomic, dietary and lifestyle factors, such as smoking and extent of salt intake, are contributing factors to gastric cancer development, but they are all subordinate to the presence of *H. pylori* infection[66,67].

Extra-gastric diseases.—Unexplained iron-deficiency anaemia, vitamin B_{12} deficiency and some cases of idiopathic thrombocytopenic purpura can be related to *H. pylori* infection[68,69]. Antigen mimicry-induced autoimmunity related to *H. pylori* has been suggested in idiopathic thrombocytopenic purpura[70,71]. Furthermore, other associations of *H. pylori* infection with diseases localized outside the stomach have been reported, including cardiovascular diseases, ischaemic heart disease, metabolic syndrome, diabetes mellitus, hepatobiliary diseases, non-alcohol fatty liver disease and neurodegenerative diseases, which have been attributed to persistent and low-grade systemic inflammation[72–74]. Most of these associations are based on limited and inconsistent data and remain inconclusive, and only a few, mostly observational, studies have documented a significant decrease in some of these manifestations when *H. pylori* is eradicated[73].

In children, particularly in the USA and Europe, an inverse association between *H. pylori* infection and asthma and allergy has been reported[75–77], although this link has not been unequivocally confirmed[78]. The often reported inverse association between *H. pylori*

infection and the risk of gastro-oesophageal reflux disease (GERD), Barrett oesophagus and oesophageal adenocarcinoma remains highly controversial[79,80], and evidence for positive and negative associations exists[79–85]. Explanations for the discrepancies might lie in differing study protocols and *H. pylori* testing methodologies as well as in heterogeneity in the selection of patient and control populations. At present, the controversial findings and debates about a potential benefit of *H. pylori* for specific clinical scenarios have no confirmation nor impact on the management of the infection[86].

Mechanisms/pathophysiology

H. pylori microbiology

H. pylori is Gram-negative, microaerophilic curved or S-shaped bacteria that are highly motile due to a unipolar bundle of sheathed flagella. The cell envelope has a characteristic Gram-negative structure, but many other components have unique features adapted to the habitat of *H. pylori* in the human stomach[2]. In comparison with many other pathogenic bacteria, *H. pylori* has a small ~1.6-Mbp genome consisting of a single circular chromosome that encodes ~1,600 proteins[87,88]. The *H. pylori* core genome consists of ~1,100 genes present in all *H. pylori* strains, whereas the remaining accessory part of the genome comprises genes variably found in strain subsets[89], for example, a large number of diverse restriction–modification systems (genetic elements that provide protection against foreign DNA), providing variable DNA methylation[90]. Extensive variation of genome content and gene sequences between strains, and even within the bacteria present in the stomach of one individual[39,91,92], is a prominent characteristic of *H. pylori* and results from the unusual combination of very high mutation and recombination rates[93]. *H. pylori* has a high mutation frequency due to lack of a classical mismatch repair pathway in combination with the pro-mutagenic properties of its DNA polymerase I[94,95]. *H. pylori* is naturally competent and can take up DNA by means of the unique ComB DNA uptake system with similarities to a type IV secretion system (T4SS)[96,97].

DNA sequence diversity can rapidly spread through *H. pylori* populations due to recombination between strains[98,99]. After import, DNA can be integrated into the chromosome based on homology, and such chromosomal imports have a unique bimodal length distribution, enabling *H. pylori* to adapt its genome to new environments in an extremely efficient way[100].

H. pylori strains show a characteristic population structure that reflects their coevolution with their human hosts and has led to conclusions about the history of its association with humans[101–103]. *H. pylori* was acquired by modern humans in Africa at least ~100,000 years ago, possibly by a host jump from an unknown animal source. The most ancestral phylogeographic population of *H. pylori* is hpAfrica2, mostly found in Southern Africa. Further important, widespread and more recently evolved populations include hpAfrica1, hpNEAfrica, hpEurope, hpEastAsia, hpAsia2 and hpSahul[104,105]. A major step in the evolution of *H. pylori* from the ancestral hpAfrica2 population to the populations that have spread over the globe was the acquisition of the *cag* pathogenicity island (*cag*PAI) by ancestral *H. pylori* from an unknown source. *cag*PAI encodes components of the Cag T4SS[106,107], which is a protein complex that spans the bacterial cell envelope and can

directly deliver diverse effector molecules into host cells following adherence. Hence, whether strains possess an active Cag T4SS has substantial effects on their interaction with hosts. c*ag*PAI-positive strains elicit far more inflammation than *cag*PAI-negative strains.

Bacterial factors involved in colonization and pathogenesis

H. pylori is highly adapted to the colonization of a unique ecological niche in the deep gastric mucus layer. Several mechanisms, including motility, urease production, adhesion and others, are important in *H. pylori* colonization (Box 1).

Motility.—Flagella-driven motility is essential for the entry of *H. pylori* into the mucus layer and for maintaining a swimming reservoir in the mucus[108] (Fig. 3). *H. pylori* has a unipolar bundle of rotating sheathed flagella, with filaments composed of two flagellin proteins[109] that evade activating the innate immune system via TLR5 due to specific adaptation of their amino acid sequences[110,111]. The direction of movement is controlled by chemotaxis and energy taxis, enabling bacteria orientation through pH and bicarbonate (and possibly other) gradients in the gastric mucus[112]. Motility can be inhibited in vitro by small molecule compounds that reduce *H. pylori* colonization density, which may be a future treatment approach[113].

Urease.—*H. pylori* produces abundant amounts of urease, aided by a unique system of accessory proteins that procure the required nickel, which is essential for urease holoenzyme activity, protects the bacterium from nickel toxicity and regulates urease activity by controlling urea influx into bacterial cells[114,115]. Urease is essential for colonization, most likely because the enzyme, by cleaving urea into ammonia and carbon dioxide, enables the bacteria to survive brief periods of exposure to very low pH values, which *H. pylori* may encounter in the gastric lumen during transmission[116]. Through urease activity, urea provides an always available nitrogen source for the organism.

Adhesion.—*H. pylori* can adhere to gastric epithelial cells by attaching surface molecules that are anchored on its outer membrane (adhesins) to host cell receptors. Adherence enables *H. pylori* to achieve high colonization despite epithelial cell shedding, mucus layer turnover and the physical force involved in gastric emptying, all of which act to reduce colonization[117]. The best-studied adhesins are encoded by members of the large *hop* superfamily of outer membrane protein-encoding genes. BabA mediates binding to Lewis b blood group antigens that are expressed on gastric epithelial cells[118]. The related SabA adhesin binds to host sialyl-Lewis x antigens, which are mainly expressed on epithelial cell surfaces under inflammatory conditions[119]. HopQ binds to multiple carcinoembryonic antigen-related cell adhesion molecules and seems to be important for Cag T4SS functionality[120,121]. AlpA and AlpB mediate binding to the extracellular matrix glycoprotein laminin[122]. Expression of adhesins varies widely between strains; the contribution of individual adhesins to bacteria–cell adherence and to pathogenesis continues to be studied.

***cag*PAI and its translocated effectors.—**The ~37-kb *cag*PAI[106] comprises ~26 genes that encode the elements of T4SS[107]. After *cag*PAI-carrying *H. pylori* attaches to a host

cell, T4SS can translocate bacterial effector molecules into the host cell cytoplasm[123], including the CagA protein, which is also encoded by the *cag*PAI. In addition, several other molecules can be translocated via T4SS, including heptose-containing lipopolysaccharide core precursors[124,125], peptidoglycan fragments[126] and bacterial DNA[127]. These molecules can interact with intracellular target molecules and profoundly affect intracellular signalling and cell function (Fig. 3).

After translocation, CagA undergoes tyrosine phosphorylation by cellular kinases[128]. The phosphorylated form can interact with multiple target molecules in the host cell, including SHP2 (ref. 129), PAR1 (refs. 130,131) and ASPP2 (ref. 132), contributing to increased cell motility, reduced cellular tight junctions, genome instability, nucleotide damage and activation of the Wnt signalling pathway that is relevant in local neoplasia formation[133]. Translocation of heptose-containing lipopolysaccharide core intermediates may be important in inducing pro-inflammatory responses by both epithelial and immune cells through the ALPK1–TIFA signalling pathway and may also induce mutagenic and oncogenic processes[134–136]. In addition, intracellular heptose signalling in macrophages may hamper antigen-presenting properties and subsequent T cell responses[136].

Vacuolating cytotoxin.—Many *H. pylori* strains secrete vacuolating cytotoxin A (VacA), which is an oligomeric autotransporter protein toxin that can form anion-selective membrane channels[137]. The effects of VacA on cells include induction of large intracellular vacuoles derived from late endosomes, induction of apoptotic cell death (following mitochondrial membrane perturbation) or necrosis, induction of autophagy, and inhibition of T cell and B cell proliferation and effects on other immune cells[138–140]. Together, these effects downregulate immune responses to *H. pylori* infection and promote host tolerance to the organism. Expression of VacA is not essential for colonization, and its contribution to illness remains controversial.

Immune responses to *H. pylori*

Innate immune evasion.—The flagellins and lipopolysaccharides of *H. pylori* have evolved substantially differently from those of other Gram-negative bacteria and are largely not recognized by the human pattern recognition receptors TLR5 and TLR4, which signal danger to the host[110,111]. These and other structural variations may contribute to immune evasion by *H. pylori* and its success as a persistent colonizer.

Innate immune activation.—Contact between *H. pylori* and gastric epithelial and myeloid cells induces signalling through multiple innate pathways, leading to changes in cellular homeostasis and the release of cytokines and chemokines that trigger local and systemic inflammatory responses[141–143]. As canonical TLR4-dependent and TLR5-dependent signalling is evaded, most inflammatory signalling depends on the activity of an intact *cag*PAI[144]. The bacterial components transported into epithelial cells through T4SS engage multiple intracellular receptors. Many of the affected pathways converge on the activation of nuclear factor (NF)-κB, which leads to increased expression and release of IL-8 and other chemokines and cytokines[145–147]. IL-8 is a powerful attractant of neutrophils, which enter the gastric mucosa and are the defining element of the active

component of chronic–active gastritis, the histological hallmark of *H. pylori* presence in the stomach[148,149]. Monocytes, macrophages and dendritic cells are also attracted to the *H. pylori*-colonized mucosa. Activation of phagocytic monocytes and macrophages seems to strongly depend on the delivery of heptose-containing lipopolysaccharide core intermediates via T4SS and the resulting signalling to the ALPK1–TIFA axis[135]. Dendritic cells can be reprogrammed by contact with the bacteria, for example, to produce IL-18, which drives the conversion of T cells to regulatory T (T_{reg}) cells, suppressing immune activation[150].

Adaptive immune response.—*H. pylori* invariably elicits a combined adaptive humoral and cellular immune response that is generally incapable of eradicating the bacteria. Colonization leads to formation of antibodies to many *H. pylori* antigens that have little effect on bacterial numbers[151]. In agreement with this apparent lack of a role of antibodies in protection against *H. pylori*, mice lacking antibody production can be successfully immunized against *H. pylori*[152]. *H. pylori* also induces the recruitment of T cells to the human gastric mucosa, including T helper 1 (T_H1), T_H17 and T_{reg} cells. Experimental vaccination in mouse models suggests that both T_H1 cells and T_H17 cells can be important in mediating protection against *H. pylori* infection[153]. Furthermore, in mouse models, a protective effect of very early (neonatal) *H. pylori* infection against asthma was mediated by T_{reg} cells accumulating in the lungs[150,154,155], consistent with the hypothesis that *H. pylori* may downregulate systemic allergic responses through its recruitment of immunosuppressive T_{reg} cells to the gastric mucosa and, potentially, other body sites such as the lung.

From chronic *H. pylori* colonization to illness

H. pylori colonization of the gastric mucosa induces a pro-inflammatory response of gastric epithelial cells, which recruits diverse immune cells to the submucosa[156]. The resulting condition is chronic–active gastritis, which is predominantly asymptomatic for decades of colonization in most patients. The severity of inflammation varies widely between individuals, depending on bacterial, host and environmental factors[157] (Box 1).

The single most important determinant of the pro-inflammatory activity of an H. pylori strain is its possession of a functional *cag*PAI[158]. Expression of additional host-interaction factors, such as a portfolio of adhesins that fits the variable host receptor makeup and promotes strong binding to epithelial cells and, therefore, promotes crosstalk between the bacterium and the host cell, contributes to the response that a strain elicits in an individual host. Tolerogenic signalling contributes to the unusual accumulation and proliferation of gastric mucosa-associated lymphoid tissue. The decades-long inflammation in the gastric mucosa is thought to be an important driving force leading to gastric atrophy and, ultimately, gastric cancer as outlined by the Correa cascade[159] (Fig. 4). The Correa cascade describes a multistage, multifactorial process starting with superficial gastritis, progressing to atrophic gastritis, intestinal metaplasia and dysplasia, and culminating in gastric adenocarcinoma. A key emerging concept is that chronic inflammation, gastric atrophy and consequent achlorhydria lead to an aberrant and dysbiotic gastric microbiome that drives the process towards gastric neoplasia[160–162]. Accumulating evidence suggests that, following H. pylori eradication, newly emerging components of the gastric microbiota might be involved in the oncogenic transformation of gastric epithelial cells[160,163]. In other individuals, peptic ulcer

disease or the rare H. pylori-associated MALT lymphoma can develop[4,5,14,164]. The reasons why most individuals remain apparently asymptomatic throughout their lifetime, whereas others proceed to clinical sequelae of varying severity, remain to be fully elucidated. Clinically useful, early bacterial predictive markers that could inform the decision to prescribe eradication therapy have not been identified.

It is now well established that the clinical outcome of *H. pylori* infection depends largely on the distribution and severity of *H. pylori*-induced gastritis[165] (Table 1). Thus, peptic ulcers are more likely in individuals with an antral-predominant pattern of gastritis characterized by high acid secretion and relative sparing of gastric corpus with its high parietal cell mass. Parietal cells secrete gastric acid and patients with peptic ulcers have a higher parietal cell mass than healthy individuals without ulcers. By contrast, gastric cancer develops in the context of corpus-predominant gastritis, gastric atrophy and a profound loss of acid secretory capacity that precedes cancer by decades[166]. The chronically inflamed and achlorhydric environment is further exacerbated by an aberrant pro-inflammatory and genotoxic gastric microbiota that drives the neoplastic process even after loss of *H. pylori* infection[160,161,167]. Indeed, experimental work suggests that transplantation of the gastric microbiota from humans with intestinal metaplasia or gastric cancer into germ-free mice leads to the development of precancerous gastric changes[168].

Diagnosis, screening and prevention

Diagnosis

Presentation.—In daily routine, acute infection with *H. pylori* remains mostly undiagnosed at any age. Naturally occurring acute infection in childhood is usually not captured and is supposed to frequently present with abdominal complaints with potentially diverse aetiologies[169]. In adults, the clinical presentation of acute infection can entail hypochlorhydria, epigastric pain and mild-to-moderate dyspeptic symptoms as described in case reports and from challenge studies in volunteers with *H. pylori* for vaccine development[170–172]. By contrast, most children with *H. pylori* infection remain asymptomatic and complications are infrequent[173].

Once established, *H. pylori* infection is a persisting and not self-limiting condition in adults with the potential of severe complications in some individuals. PUD, gastric cancer and MALT lymphoma[174], in decreasing order of incidence, are the most important complications in adults[86].

Diagnostic tests.—An accurate diagnosis of *H. pylori* infection is required before commencing treatment[42,175]. Diagnostic methods for *H. pylori* detection include invasive and non-invasive test procedures[70,176–181] (Fig. 5) (Tables 2 and 3).

Invasive tests require biopsy samples obtained during gastroduo-denoscopy and include the rapid urease test (RUT), histological assessment, bacterial culture and direct detection of *H. pylori* genetic material using PCR, quantitative PCR or fluorescence in situ hybridization. Non-invasive methods include the ^{13}C-urea breath test (UBT), serological detection for

anti-*H. pylori* antibodies, the stool antigen test (SAT) and direct detection of *H. pylori* genetic material in stool via PCR[179].

RUT is a low-cost test with a specificity of 95–100%. False positive results are rare and can be explained by the presence of other urease-positive organisms such as *Proteus mirabilis*[179]. Current use of a proton pump inhibitor (PPI) may lead to false negative results in RUT as well as in all other diagnostic tests except for serological assessment[175]. Thus, PPI therapy should be interrupted 14 days before testing[42].

Histological assessment on formalin-embedded samples is made according to the updated Sydney system, which provides information on *H. pylori* presence via direct visualization and on the extent of active and chronic inflammation and atrophy[148,149,182]. The histochemical method for assessment of *H. pylori* gastritis relies on haematoxylin and eosin and Giemsa stains for detection of *H. pylori*[148]. Gastritis severity is defined by the degree and extension of atrophy and/or intestinal metaplasia. Severe gastric atrophy is associated with an increased risk of gastric cancer and risk is best determined by changes according to the gastritis severity staging systems Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis/Intestinal Metaplasia Assessment (OLGIM)[183,184].

Culture of *H. pylori* is 100% specific but has a relatively low sensitivity (<80%) strongly dependent on transport media and logistics and laboratory proficiency owing to the required laboratory expertise with special culture media. Limitations include costs and time constraints but microbial culture also enables phenotypical antimicrobial susceptibility testing (AST)[180].

Molecular testing from formalin-embedded biopsy or RUT samples with PCR methods, of which quantitative PCR is most appropriate, and fluorescence in situ hybridization is highly accurate in the detection of *H. pylori*[185] and can also be combined with molecular resistance testing[186].

Serological assessment of serum IgG levels is used as a screening test in specific clinical scenarios but it cannot distinguish active and previous infections because of the prolonged persistence of *H. pylori* antibodies. A positive serological test should be confirmed with a test that indicates active infection[187]. Serological testing is the only method not influenced by current PPI intake. Next-generation blood tests to be used for screening in the consulting room became available in 2022 (ref. 187).

UBT uses stable isotope-labelled ^{13}C-urea ingested with citric acid, which is then hydrolysed by bacterial urease and releases carbon dioxide and ammonia. UBT has high sensitivity and specificity (95–100%)[181]. SAT has a similar diagnostic accuracy as UBT. SAT is an immunological method based on monoclonal antibodies with which *H. pylori* antigens can be detected in stool samples[180]. UBT, SAT and histological assessment are the commonly used tests in clinical practice for diagnosis of *H. pylori* as they enable the detection of active infection. However, the availability of these tests depends on the status of regional health-care services, which can directly affect treatment decisions[175,179].

The increase of antibiotic resistance to *H. pylori* worldwide[188,189] demands AST in the individual patient to enable effective therapy choices following failed eradication treatment and to monitor antimicrobial resistance at the regional community level[42]. AST can be performed using phenotypic and genotypic approaches. Culture-based phenotypic testing requires fresh biopsy samples, but PCR-based genotypic testing can be done on fresh, formalin-embedded or RUT samples as well as on stool samples[186,190–192]. Clarithromycin resistance should be excluded before its empirical use in regions with known clarithromycin resistance rates of >15% or unknown resistance rates[42]. Molecular genotypic testing enables the detection of resistance against frequently used antibiotics. Clarithromycin resistance conferred by mutations in the gene encoding 23S rRNA are predominantly related to A2143G, A2142G and A2142C[193]. Levofloxacin resistance is conferred by point mutations in the gyrase gene *gyrA*[194,195]. The accuracy of the molecular detection methods for predicting antibiotic resistance varies between antibiotics, favouring clarithromycin and quinolone resistance detection[194,196]. Formalin-embedded biopsy samples enable genotypical resistance testing at a later time point after endoscopy[197–200].

Infections with *Helicobacter* species other than *H. pylori* are rare and those most relevant refer to *Helicobacter heilmannii*, *Helicobacter felis* and *Helicobacter suis*[201–203]. Standard *H. pylori* diagnostic tests (UBT, SAT, serological assessment and immunohistochemistry) have low sensitivity for the detection of these species[201]. The clinical relevance of these often incidentally detected rare infections is low because of the low rates of complications.

Testing for eradication success after 4–6 weeks of antibiotic treatment is primarily — with some specific exceptions — performed with non-invasive diagnostic tests UBT and SAT (see Management section)[42]. PPI use has to be stopped 14 days before testing to exclude recrudescence of reduced bacterial density under acid suppressive therapy.

Indications for diagnostic testing.—Based on the rarity of complications in childhood, a diagnostic endoscopic examination and treatment is recommended only in those with suspected peptic ulcer disease[169]. In general, *H. pylori* detection in children is only recommended when complications arise[169,204]. In the group of patients with dyspepsia without alarm symptoms, such as anaemia, loss of weight or family history of gastric cancer, and age <45 years (45–55 years according to age-related gastric cancer incidence variation among world regions), non-invasive testing with UBT or SAT is the strategy of choice[70,205,206]. In patients aged >45 years or in the presence of alarm symptoms, endoscopy-based diagnosis is recommended to exclude mucosal changes[207,208]. *H. pylori*associated dyspepsia is an independent entity that resembles but is distinct from functional dyspepsia[1,208]. A test-and-treat strategy is the most cost-effective approach in patients with *H. pylori* infection and dyspepsia if *H. pylori* prevalence in the population is >5%. This strategy is superior to alternative therapies including PPIs[70,209,210], and the therapeutic gain of *H. pylori* eradication for symptom relief compared with other therapeutic options is substantial. A randomized, double-blind, placebo-controlled trial for primary prevention of peptic ulcer bleeding in older patients who were prescribed aspirin in primary care lends support to an *H. pylori* test-and-treat strategy in patients starting aspirin treatment. Gastrointestinal bleeding episodes within a 2-year period were reduced by 65% in the *H. pylori* eradication group[211].

Screening and prevention

***H. pylori* eradication as a strategy for preventing gastric cancer.—**Gastric cancer incidence and mortality at the population level are reduced by *H. pylori* eradication but more epidemiological data are required. Meta-analyses of randomized controlled trials and observational studies have concluded that moderate evidence suggests that *H. pylori* eradication therapy reduces the incidence of gastric cancer in healthy individuals[212,213], with an overall risk reduction of 46%[212]. In individuals with *H. pylori* infection and a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduces the risk of gastric cancer, with an overall risk reduction of 55%[214]. A meta-analysis of randomized and observational cohorts that included five studies that considered baseline histological findings suggests that *H. pylori* eradication seems to be a primary preventive strategy in individuals with non-atrophic gastritis or multifocal atrophic gastritis without intestinal metaplasia, but not in those with intestinal metaplasia or dysplasia[215]. In another meta-analysis, *H. pylori* eradication was associated with improvement in the severity of atrophic gastritis with and without intestinal metaplasia compared with placebo[216]. Notably, eradicating *H. pylori* in patients treated for early-stage gastric cancer reduces rates of metachronous gastric cancer by ~50% (range 20–70%) according to two meta-analyses of randomized trials[217,218]. In a pivotal trial, the reduction in metachronous gastric cancer incidence following endoscopic removal of early gastric cancer in patients receiving *H. pylori* eradication compared to placebo[219] suggests that eradication therapy may even work in the condition of severe atrophic gastritis[220].

Diffuse and intestinal types of gastric cancer[221] are two major histological entities that differ in epidemiology, pathogenesis and clinical course[222]. However, randomized and observational studies have been unable to separately calculate the risk effects for these histological types. Further data on the benefits or adverse effects of *H. pylori* eradication will come from ongoing trials in China[223], UK (HPSS study)[224], Korea (HELPER Study)[224] and Latvia (GISTAR study)[225].

Targeted test-and-treat strategies for *H. pylori* infection.—*H. pylori* test-and-treat strategies aim to decrease morbidity and mortality related to gastroduodenal disease (Box 2) according to the 2022 Maastricht VI/Florence guidelines[86]. This strategy is appropriate for individuals with non-investigated dyspepsia. Testing for *H. pylori* infection should also be performed in persons who use NSAIDs and have a history of peptic ulcer. In addition, evidence is accumulating that supports the eradication of *H. pylori* in individuals with non-ulcer dyspepsia[226], idiopathic thrombocytopenic purpura[227], and iron and vitamin B_{12} deficiency anaemia[228,229]. Consensus exists for eradicating *H. pylori* in all cases of MALT lymphoma, regardless of disease stage and prognostic factors[230,231]. Cure of *H. pylori* infection results in complete histological remission in most patients with localized MALT lymphoma[232].

Serological assessment for gastric cancer screening.—A large body of research, particularly from East Asian populations at high risk, suggests that measurement of circulating pepsinogen levels is the most useful non-invasive test to define the status of the gastric mucosa (that is, whether it is atrophic)[233,234]. Experts from the Kyoto Global

Consensus agreed that pepsinogen levels in conjunction with anti-*H. pylori* antibody levels are useful for identifying individuals at increased risk for gastric cancer[1]. Although there are still possibilities for optimization, the ABC (gastritis A, B, C and D) screening method based on this combined measurement is useful for the detection of an increased risk for both intestinal and diffuse types of gastric cancer[235]. The specific groups are defined as follows, where Hp indicates *H. pylori* infection and PG indicates pepsinogen: A [$Hp^{-}PG^{-}$], individuals without infection; B [$Hp^{+}PG^{-}$], without chronic atrophic gastritis (CAG); C [$Hp^{+}PG^{+}$], with CAG; and D [$Hp^{-}PG^{+}$], with severe CAG; the latter two groups carry the highest risk for gastric cancer[236,237].

Population endoscopic screening for gastric cancer.—Around 75% of all new gastric cancer cases are diagnosed in East Asian populations[238]. Consequently, Japan and South Korea have established successful national screening programmes in individuals aged ≥40 years using either upper gastrointestinal series or upper endoscopy, depending on participant preference or comorbidities. Endoscopy has been the primary method for gastric cancer screening in Japan since 2017, and a study published in 2022 reported the benefits of this approach in the reduction of gastric cancer mortality[239]. In South Korea, the use of upper endoscopy has increased as this method is more accurate than upper gastrointestinal series for gastric cancer screening[240].

Endoscopic surveillance of individuals at high risk.—Although *H. pylori* eradication can reverse multifocal gastric atrophy and, to some extent, intestinal metaplasia, some patients with these histological lesions might benefit from surveillance at regular intervals. According to the management of precancerous conditions and lesions in the stomach (MAPS II)[241] European guidelines and the Maastricht VI/Florence consensus[86], individuals with advanced stages of atrophic gastritis (severe atrophic changes with and without intestinal metaplasia in both antrum and corpus, OLGA/OLGIM stages III and IV) should be followed-up with a high-quality endoscopy every 3 years. Based on growing evidence, endoscopic surveillance should also be considered in individuals with intestinal metaplasia at a single location but with a family history of gastric cancer, in those with incomplete-type intestinal metaplasia and in those with persistent *H. pylori* gastritis. These recommendations are primarily intended for regions with low-to-moderate gastric cancer burden, where population-based screening is not practical or economically feasible but where subgroups at risk can be identified. Although the American Gastroenterological Association does not recommend routine use of endoscopic surveillance in patients with intestinal metaplasia[242], a common denominator between American Gastroenterological Association and European MAPS II guidelines is that they are based on low-quality evidence, highlighting the need for well-designed, large and long-term trials.

Management

General aspects

H. pylori gastritis is an infectious disease and all adult individuals with the infection require therapy for cure if clinical symptoms and complications are present or for prevention if at risk for complications even if asymptomatic[1,42,243]. *H. pylori* test-and-treat strategies are

selected according to diverse clinical scenarios[17,42,206] (Box 2). In the paediatric population, *H. pylori* infection rarely leads to complications and requires specific management addressed in the joint ESPGHAN/NASPGHAN Guidelines that were updated in 2016 (ref. 169). All treatment discussions in this section relate to the disease in adults.

Treatment regimens for *H. pylori* eradication are based on the combination of a strong acid suppressant and antibiotics. First-line therapy is selected according to locoregional or individual *H. pylori* antibiotic resistance patterns[244,245]. Treatment failures induce resistance to several of the antibiotics used in first-line regimens and render further therapies more complex and costly[42,206,246,247]. Second-line therapy needs to consider the first-line regimen and antibiotic resistance status (Fig. 6). Confirmation of treatment success not earlier than 4 weeks after end of therapy is mandatory to guide further management and provides important information on the effectiveness of treatment regimens in defined regions[42].

PPI triple therapy

First-line setting.—The introduction of PPI-based triple therapies (PPI-TT) marked a turning point in the treatment of *H. pylori* infection owing to their superior efficacy compared with previous approaches. The three components of PPI-TT include a PPI, clarithromycin and amoxicillin or, alternatively, metronidazole as a substitute for either amoxicillin or clarithromycin. Seven-day PPI-TT obtained initial eradication rates of >90%[248,249] and, between 1997 and 2005, became the most widely recommended first-line therapy globally[42,206,247,250]. Treatment duration has since been recommended to be extended to 14 days owing to a substantially higher efficacy compared to the 7-day duration[42,244,247]. Antibiotics used in first-line PPI-TT are clarithromycin, amoxicillin and metronidazole or, more restrictive, levofloxacin and, in selected cases, furazolidone. Treatment failures with PPI-TT occur with increasing frequency and are primarily related to antibiotic resistance, insufficient acid suppression and inadequate adherence to medications[10,251–253]. Acid suppression with PPI (omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole in double standard dose) is essential and aims to raise intragastric pH to 6 or higher, which optimizes the stability, bioavailability and efficacy of antibiotics[254,255]. A modestly higher acid-inhibiting effect is shown for second-generation PPIs (esomeprazole, rabeprazole)[256]. Increased intragastric pH (optimum pH >6) enables bacterial replication, which increases the susceptibility of *H. pylori* to antibiotics. This is particularly important for amoxicillin, which is highly acid sensitive[254,255]. Less effective acid suppressants, such as histamine 2 receptor antagonists, are no longer considered in *H. pylori* eradication regimens[246,257]. PPI efficacy is further increased by doubling the PPI standard dose and should always be considered if first-line therapy fails[258–261].

Rapid metabolization of PPIs leads to reduced efficacy[253,262,263]. Rapid and ultrarapid metabolization of PPIs varies considerably among ethnic groups and occurs more frequently in white and African American populations, whereas slow metabolization is more frequent in Asian, including Japanese and Chinese, populations[264–267]. The efficacy of PPI metabolism depends on various genetic mutations related to CYP2C19 polymorphism and, to a minor extent, on CYP3A4 and gastric H^+,K^+-ATPase genotypes[255,268]. Apart from the use of PPI double standard dose in rapid metabolizers, better control of acidity has been

reported by increasing PPI dosing frequency up to four times or by switching to a PPI less influenced by CYP2C19 genotypes[268–271]. No guideline is yet available recommending CYP2C19 genotyping to guide PPI prescription in clinical practice. The pharmacokinetic and pharmacodynamic properties of the second-generation PPIs esomeprazole and, in particular, rabeprazole are less influenced by variant CYP2C19 genotypes[268,270,272,273].

To overcome inadequate adherence, careful patient instruction is appropriate on how to take medications and how to proceed in case of adverse events[274,275]. A history of penicillin allergy, availability of susceptibility testing, local prevalence of antibiotic resistance and history of prior eradication therapies should be considered when deciding on the initial therapy (Fig. 6).

Antibiotic resistance.—Antibiotic resistance is the most important factor in PPI-TT failure[244]. Clarithromycin resistance and metronidazole resistance are the most relevant resistances for PPI-TT failure[42,247,276]. Clarithromycin resistance has increased from 3% to 11% around the turn of the century and is now up to 15–30% worldwide[188,189,248,277–279]. In 2,852 treatment-naive patients from a European registry on *H. pylori* management (Hp-EuReg), resistance to clarithromycin, metronidazole and levofloxacin were 25%, 30% and 20%, respectively[261,278]. Resistances to tetracycline and amoxicillin were <1% in the same study. A WHO global priority list qualifies clarithromycin-resistant *H. pylori* infection as a high threat among community-acquired infections[280], and international guidelines recommend abandoning clarithromycin-based regimens if regional resistance exceeds 15%[244].

Among several modifications developed to overcome clarithromycin resistance, including sequential therapy (PPI-dual followed by PPI-TT) and hybrid therapy (PPI plus three antibiotics), only concomitant therapy (PPI plus three antibiotics simultaneously administered)[244,281–283] was found to be superior to clarithromycin-based PPI-TT[281,282]. Concomitant therapy as an empirical first-line option should cautiously be considered in regions of clarithromycin resistance >15% and only used if individual AST or bismuth-based quadruple therapy (BiQT) are not locally available[42,247,250]. Levofloxacin as a component of PPI-TT is effective in first-line and second-line regimens in regions with low levofloxacin resistance[284–286]. However, levofloxacin resistance is now up to 20% in Europe and 18% in the Asia-Pacific region[188,278,287]. Although levofloxacin is not recommended as a first-line option, the high resistance restricts its use even in second-line regimens[42,244,247]. AST before using levofloxacin in empirical second-line regimens is advised[189,244,278,287]. Other quinolones, such as ciprofloxacin and moxifloxacin, which have reduced efficacy and/or less consistent results, are not an alternative to levofloxacin[286,288]. Sitafloxacin-based triple and dual regimens that have been successfully tested in Japan[289] are not used as an alternative to levofloxacin in western countries[42,244,247.]

Metronidazole resistance is >25% in most areas of the world[189,278] but has a minor effect on eradication efficacy when used in triple or quadruple regimens because of inconsistency between in vitro AST results and clinical efficacy and the synergism with co-administered drugs, in particular bismuth[224,290,291]. Resistance to amoxicillin and tetracycline is low (<2%) and these antibiotics remain a key component in standard PPI-TT and in BiQT,

respectively, without the need for routine AST[244,291]. Rifabutin resistance is <1% and the *H. pylori* eradication rate of rifabutin-containing regimens is 73% according to a meta-analysis from 2020 (ref. 292). A rifabutin delayed-release preparation, combined with amoxicillin and omeprazole, obtained an eradication rate of 89%[293] and FDA approval for use as a first-line therapy was granted in 2019 (ref. 294). Outside of the USA, rifabutin-containing regimens are recommended as rescue therapy only owing to the need of this drug for other critical infections and the risk of myelotoxicity in rare cases[42,247]. Furazolidone resistance is <5% and the drug is effective in triple and quadruple combinations; its use is limited to a few countries in Asia and South America[195,295] and it may serve as rescue therapy in individual cases[296].

For these antibiotic classes, mechanisms of resistance are related to drug-specific target gene mutations (macrolides and quinolones) or to detoxication (nitroimidazoles)[296]. *H. pylori* colonies may carry single-drug, multidrug or hetero resistance[296,297]. Isolates from antrum and corpus are reported to differ by up to 15% in AST, which may account for treatment failure if biopsy samples for AST are only taken from a single site in the stomach[298,299].

Bismuth-based quadruple therapy

Bismuth has multiple beneficial properties in peptic ulcer healing that include a stimulating effect on prostaglandin synthesis, inactivation of pepsin, and bile acid binding but, most relevant in *H. pylori* eradication, is its bactericidal effect[300,301]. Bismuth subcitrate upregulates the expression of genes involved in *H. pylori* growth and metabolism and impedes proton entry, thereby preventing lowering of the bacterial cytoplasmic pH. These mechanisms are suggested to render antibiotics more effective[302]. Bismuth-based quadruple therapy (BiQT; PPI, bismuth, tetracycline and a nitroimidazole antibiotic), available either as individual components or as PPI plus a capsule containing all antibacterial components, has an eradication efficacy of 90%[261,291,303,304].

BiQT is recommended as an empirical first-line therapy, does not require AST, is not affected by clarithromycin resistance and overcomes metronidazole resistance owing to synergism with bismuth, as documented by its consistently high therapeutic efficacy[244,291,300]. Bismuth added to clarithromycin-containing regimens increases eradication efficacy also in the presence of clarithromycin resistance but, in these combinations, offers no advantage over standard BiQT[300,305,306]. BiQT does not contain antibiotics that are essential for cure of other infections. BiQT is an effective rescue option with a success rate of >90% following previous treatment failures[303,307,308].

Regimens with potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs), a new class of acid inhibitors, have a more potent and durable effect on acid suppression than PPIs[309,310]. Vonoprazan-based triple therapy (V-TT) with clarithromycin and amoxicillin in first-line achieved an eradication rate of 92.6% versus 75.9% with PPI-TT, and 98% in second-line in Japan[311], which was also confirmed in western countries[312]. In network meta-analyses, V-TT ranked best among all current first-line empirical therapies, which was also confirmed after the inclusion of a trial conducted in western countries[313,314]. Vonoprazan dual therapy, consisting of vonoprazan

plus amoxicillin, provides an eradication rate of *H. pylori* similar to that of V-TT[252]. Increasing resistance and absence of new antibiotics set major expectations on P-CAB-based regimens, which are being investigated in several trials[309] (Supplementary Table 1).

H. pylori eradication and rescue therapies

Management of refractory *H. pylori* needs to consider individual or local antibiotic resistance, facilities for AST, logistics, and drug availability[244,246] (Fig. 6). Following PPI-TT failure, BiQT or a regimen with antibiotics selected following AST is recommended[42,244,247]. Empirical therapy, with careful consideration of previously taken medications, is a valid alternative to genotypic resistance-guided therapy of refractory *H. pylori* infection[315]. BiQT is currently the best empirical approach as it is not influenced by antibiotic resistance[316]. If BiQT fails in first-line, levofloxacin-based triple therapy is recommended. A meta-analysis including 25 trials with levofloxacin-based triple therapy in second-line treatment reports a cumulative eradication rate of 74.5% (95% CI 70.9–77.8)[317]. The PPI-amoxicillin, high-dose, dual therapy is another option, with a ≥81% eradication rate achieved as second-line treatment and with an efficacy comparable to other recommended therapies[318,319].

P-CABs in triple therapies and in dual combination with amoxicillin already effectively used in Asian countries will become an important option once generally available and properly adapted to regional demands in first-line and second-line eradication regimens[311,313]. Rifabutin-based triple therapy is well documented as effective and should be kept as rescue therapy[292]. Surveillance programmes at the regional level, the introduction of antibiotic stewardship, regulations in the use of antimicrobials and increased public awareness are advised to control the increasing resistance of *H. pylori*[244,320,321].

Adverse events

Overall, eradication regimens have a favourable safety profile, with usually mild and very few severe adverse events. Mostly mild-to-moderate adverse effects occur in 30–70% of patients and include taste disturbances, nausea, headache, diarrhoea and non-specific gastrointestinal symptoms with some variations according to type of eradication therapy[282,291,322–324].

Diarrhoea varies in prevalence from >1% to 15% according to definitions applied, the population treated and type of therapy[325]. The non-recording of adverse effects as primary criteria in clinical trials accounts for the high variations. Darkening of the tongue and faeces is characteristic of bismuth salts[326]. Antibiotics affect gut microbiota and lead to mostly transient dysbiosis, bacterial resistance and overgrowth of opportunistic pathogens; however, rarely of *Clostridioides difficile*[40,325,327].

Probiotics added to *H. pylori* therapies have a small and inconsistent effect on eradication rates but reduce adverse effects[42], which has been shown in meta-analyses for individual probiotics as well as for mixtures[322,328,329]. In a new randomized controlled study, *Saccharomyces boulardii* combined with a mixture of probiotic bacteria modestly increased the eradication efficacy and reduced adverse effects[330], whereas *S. boulardii* alone had no effect on eradication but remained effective in reducing adverse effects such as severe

diarrhoea[331]. Defined probiotic mixtures have been shown to antagonize the harmful effects of antibiotics on the gut microbiota and their metabolic functions[325].

Effects on peptic ulcer and MALT lymphoma

Successful *H. pylori* eradication achieves ulcer healing rates of >90% and continued acid inhibition with PPI is not required for uncomplicated duodenal ulcer[42]. Gastric ulcer requires prolonged acid inhibition for healing and endoscopic follow-up is needed to ensure complete ulcer healing and to exclude underlying gastric malignancy[332]. Management of bleeding peptic ulcers, both duodenal and gastric ulcers, requires immediate care by controlling and/or restoring cardiocirculatory and respiratory function and by performing emergency diagnostic endoscopic examination and endoscopic interventions according to standardized protocols[333,334]. PPI treatment is continued until complete healing is endoscopically documented[44]. *H. pylori* eradication should be initiated after the active bleeding phase is under control and oral nutrition can be resumed[70,334]. Patients with *H. pylori* infection exposed to ulcerogenic medications, in particular NSAIDs, are at an increased risk of complications[56,335] and benefit from *H. pylori* testing and treatment[42,70]. Patients at high risk for rebleeding after *H. pylori* eradication, for example, those with continued NSAID use, require PPI maintenance therapy[336].

H. pylori eradication is the standard-of-care initial therapy for MALT lymphomas in all stages and obtains 70–80% long-term remission in stage I disease[337,338]. Eradication therapy in patients negative for *H. pylori* after exclusion of the infection with routine diagnostics obtains cure in 30% of patients and should, therefore, always be considered as a first management step[339].

Quality of life

Despite the vast number of *H. pylori* treatment studies, surprisingly few investigations have measured quality of life (QoL) outcomes. Several different questionnaires have been used to ascertain QoL metrics across the spectrum of diseases associated with *H. pylori*, and results have shown that eradication of *H. pylori* can either improve or worsen QoL, which may depend on the type of treatment used[340]. In a study from Japan, participants were included to survey improvement of GERD-related QoL measures following *H. pylori* treatment using a Japanese version of the QoL in reflux and dyspepsia score (QOLRAD-J) and Carlsson–Dent questionnaires[341]. GERD-related QoL scores improved following treatment and these were magnified among individuals with severe reflux symptoms. In another study, an 8-item Short-Form Health Survey and a modified Frequency Scale for GERD symptoms were used following *H. pylori* eradication[342]; QoL improved irrespective of treatment outcome. Finally, in a study from Thailand, patients with functional dyspepsia indicated that *H. pylori* infection, anxiety or depression were common, occurring in 23.3%, 23% and 7.3% of patients, respectively[343]. These findings suggest that eradication of *H. pylori* might not only improve functional dyspepsia but also potentially prevent the development of gastric cancer in some patients with functional dyspepsia by eliminating the chronic inflammatory process in the stomach.

In the UK, a randomized controlled study of QoL was conducted in 39,929 patients with dyspepsia following *H. pylori* therapy using a validated dyspepsia questionnaire and the psychological well-being index (PGWB) and reported no effect on QoL following therapy[344]. A further study in a smaller number of patients with functional dyspepsia similarly noted no improvement in QoL after eradication[345]. Other studies from Europe have reached different conclusions. In a study from Hungary, using the Functional Digestive Disorder Quality of Life system adapted from France to determine QoL in patients with functional dyspepsia, improvement of QoL was dependent on *H. pylori* therapy[346]. In a study from Croatia, the Gastrointestinal Symptom Rating Scale questionnaire was employed and improvement in QoL of patients with dyspepsia was found as early as 1 month into the year-long study[347].

A group from Africa used the Short-Form Leeds Dyspepsia Questionnaire and the Short-Form Nepean Dyspepsia Index in health-care workers with dyspepsia and found reduced QoL in those with high dyspepsia prevalence[348]. In a study from Rwanda, dyspepsia was assessed within the general population using the Short-Form Nepean Dyspepsia Index questionnaire and noted improved QoL, which was dependent on *H. pylori* treatment[349].

Finally, in a study examining potential detrimental consequences of eradication therapy, it was reported that patients with a duodenal ulcer in whom *H. pylori* eradication was successful were more likely to develop oesophagitis in the first year after treatment than those without *H. pylori* eradication[350]; however, in the subsequent 2 years, there was no difference between the groups. Collectively, these disparate results probably reflect differences in *H. pylori* treatment regimens, the QoL scoring systems used, varying genetic backgrounds of the host populations and differences in infecting *H. pylori* strains[350].

Outlook

A vision for the future is to provide a healthy stomach free from *H. pylori* to all individuals. The expectation that *H. pylori* incidence will decrease to the point that the bacterium will disappear spontaneously within a foreseeable time frame is unlikely to occur[351]. A population-wide test-and-treat strategy should therefore remain a consideration. This strategy could confer a health benefit with the prevention of *H. pylori*-related complications in a considerable number of individuals. However, logistic limitations, substantial health costs and risks related to the massive use of antibiotics with the fear of aggravating antibiotic resistance would be disadvantages. Thus, the identification of individuals and population subsets with a higher-than-average risk of gastric cancer should be, for now, the primary target in prevention strategies. This is the case for first-degree family members of patients with gastric cancer and populations in world regions with high gastric cancer incidence. This approach is supported by favourable cost-effectiveness and advised by expert consensus reports and guidelines[17,86]. A new concept for comprehensive intrafamilial *H. pylori* management has been proposed for regions of high *H. pylori* prevalence[352]. It advises actively proceeding with test-and-treat strategies in family members living in the same household as the index patient diagnosed with *H. pylori* based on the rationale of predominant intrafamilial spreading of the infection, mainly in childhood.

Antibiotic resistance, with its dramatic increase, demands new antimicrobial drugs that can specifically target *H. pylori* and avoid cross-resistance effects and induction of antibiotic resistance in *H. pylori* and other bacteria (Box 3). Colloidal bismuth subcitrate remains a candidate, with a direct bactericidal effect by inducing cellular swelling, vacuolization, structural degradation and cell wall eruption of *H. pylori*[353]. For now, bismuth has the limitation of cure rates of <20% if used as monotherapy[301].

Urease is an essential factor for the survival of *H. pylori* in the acidic gastric environment, producing ammonia and carbonic acid to neutralize the acidic surroundings[354]. However, urease is a complex target composed of two subunits with 12 active sites[354]. The delineated structure of the proton-gated urea channel of urease[355] and the development of a drug that can block the rapid influx of urea into the bacterium may offer a solution to inhibit the activity of urease.

Inhibition of motility by blocking the flagellar function of *H. pylori* might be worth considering as a therapeutic target. *H. pylori* flagella enable rapid movement through the viscous mucus, and disruption of a gene encoding cardiolipin synthase of *H. pylori* strain G27, shown in vitro, may abolish the biosynthesis of flagellum[356]. Furthermore, interference with the outer membrane proteins of *H. pylori* that confer adhesion to host glycans, mucins or gastric mucosa, such as BabA and SabA[357], may impair *H. pylori* survival in the gastric mucosa. An anti-adhesion nanomedicine composed of *H. pylori*-mimicking outer membrane nanoparticles could compete with *H. pylori* and reduce its adhesion to gastric epithelial cells[358].

Another approach is to increase the penetration of drugs into the gastric mucus layer, which includes the loosely adherent and firmly adherent mucus layers[359]. Conventional mucoadhesive particles usually attach to the loosely adherent layer only and are easily moved downstream to the lumen upon peristalsis[359]. Some potential mucuspenetrating polymeric nanoparticles can penetrate into the firmly adherent mucus layer[359]. Thus, delivery of selective antibiotics or other agents against *H. pylori* may be rendered more effective through the development of polymeric nanoparticles. *H. pylori* is a microaerobic organism and susceptible to increased oxygen levels, thus, the delivery of nanoparticles that include oxygen into the gastric mucus layer could render the bacterium vulnerable. In addition, multiple aspects of the interaction of *H. pylori* with the gastrointestinal microbiome are addressed by current research and will influence future research[360–364]. The exclusive property of *H. pylori* to colonize and infect the gastric mucosa affects the biodiversity of other gastric bacteria and their role in either enhancing or mitigating *H. pylori*-induced gastric inflammation; this needs to be further explored. *H. pylori* dominates the mucosa-associated community in the stomach but is less influential on the composition of bacterial communities in gastric juice[365]. In individuals with *H. pylori* infection, and even following eradication, the gastric microbial composition is dependent on the extent of gastric mucosal damage previously induced by *H. pylori* and gastric acidity[366,367]. In patients with atrophic gastritis, bacterial clusters comprising *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella*, *Rothia* and *Granulicatella* with carcinogenetic potential become predominant, whereas the probiotic *Faecalibacterium prausnitzii* is depleted[367]. The development of targeted probiotics in the direction of antagonizing carcinogenic clusters

in patients with atrophic gastritis following *H. pylori* eradication will serve an important purpose. It will be a further point of interest to understand the role of bacteria carried in the saliva and transiting the stomach and whether, in the absence of *H. pylori*, some of them become candidates for resilience and explain the entity of *H. pylori*-negative gastritis. The contributing role of bacteria in the development of severe gastritis into gastric cancer is shown in animal experiments and humans, and more insights are expected in this area[161,368,369]. Vaccine development should be pursued and lessons from previous failures will help in new approaches[172].

Field and challenge studies should both be conducted after identification of effective vaccine candidates. A vaccine for preventive and therapeutic purposes might consider multiple epitopes to direct the immune response towards essential *H. pylori* functions such as epithelial cell adherence, proliferation and survival in the specific gastric niche[230,370]. Preliminary evidence shows that *H. pylori* reduces the efficacy of treatment with immune-checkpoint inhibitors in malignant diseases[371,372]. If these findings are confirmed in further investigations, a test-and-treat strategy for *H. pylori* could become a requirement before starting immune therapies in oncological diseases. Immune mechanisms involved in this phenomenon deserve further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Bacterial, environmental and host factors contributing to *H. pylori*-induced gastric cancer pathogenesis

Bacterial virulence factors

- Cag type IV secretion system[106,123,167]
- *vacA* allelic genotypes linked to disease, for example, s1/m1/i1 alleles[139,165]
- Adhesins, for example, BabA, SabA and HopQ[118–120]

Environmental factors

- Smoking
- Dietary factors (low iron, high salt, and/or low fresh fruit and vegetable intake)[167,383]

Host genetic factors

- Single-nucleotide polymorphisms in cytokine and growth factor genes encoding proteins that have been implicated in pathogenesis (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IL-17A/B, IFNγ, TNF, TGFβ) and their receptors (IL-RN, TGFR), innate immune receptors shown to be activated by *Helicobacter pylori* (TLR2, TLR4, CD14, NOD1, NOD2), enzymes involved in signal transduction cascades (PLCE1, PKLR, PRKAA1), glycoproteins (MUC1, PSCA) and DNA repair enzymes (ERCC2, XRCC1, XRCC3)[29,387]

Gastric inflammatory phenotypes and associated gastric functions[165–167]

- Corpus-predominant gastritis
- Atrophic gastritis (Operative Link on Gastritis Assessment (OLGA) III–IV)
- Hypochlorhydria
- High gastrin levels
- Low pepsinogen I levels and ratio of pepsinogen I to pepsinogen II

Gastric dysbiosis of microbes other than *H. pylori*[160,364,384]

Box 2

Test-and-treat or endoscopy-based diagnosis in clinical management of *H. pylori* infection

Test-and-treat

This strategy refers to non-invasive testing of patients with dyspeptic symptoms and without alarm symptoms, such as vomiting, weight loss or anaemia, at age 50 years (range 45–55 years because of increased individual risk of gastric cancer). The non-invasive ^{13}C-urea breath test or stool antigen test are highly accurate in diagnosing current *Helicobacter pylori* infection[376] and surrogate markers for the histological detection of *H. pylori* gastritis. Serious upper gastrointestinal lesions in patients with dyspepsia in this age group are very rare; thus, non-invasive testing as an initial management step is appropriate in areas of low or intermediate gastric cancer risk[388,389]. Test-and-treat is superior to other management options, including empirical proton pump inhibitor therapy in patients with dyspepsia, and is more cost-effective than empirical therapy and endoscopy-based management[390,391].

Endoscopy-based diagnosis

This approach is required to exclude gastric preneoplastic conditions or malignant disease in patients with dyspeptic or other symptoms referred to the upper abdomen at age >50 years or at any age in the presence of alarm symptoms. A patient with symptoms related to ulcerogenic drug (NSAIDs) use should also be considered for endoscopy[70,392]. Endoscopy-based investigations are the most reassuring and should be considered in patients with anxiety[393].

Test-and-treat for gastric cancer prevention

This strategy targets asymptomatic individuals at increased risk of gastric cancer owing to a first-degree relative with this malignancy. The non-invasive ^{13}C-urea breath test or stool antigen test are appropriate for younger adults. Endoscopy-based investigations should be considered in individuals >45 years of age or earlier according to the age at which gastric cancer was diagnosed in the index patient[394].

Population-based test-and-treat

This approach is recommended in regions with a high gastric cancer incidence. For this purpose, serological assessment combining the detection of anti-*H. pylori* antibodies with measurement of pepsinogen levels provides useful information on the aetiology and atrophy stage of chronic gastritis and helps direct further management of the disease[17,395,396].

Box 3

Potential therapeutic targets for non-antibiotic drugs against *H. pylori* infection

Urease

Block the proton-gated urea channel, inhibit the activity of urease and block the production of urease.

Flagella

Inhibit motility, impair structure and production of flagella.

Adhesion factors

Reduce the adhesion of *Helicobacter pylori* to gastric mucosa.

Drug delivery into gastric mucus

Increase the delivery of antibiotics or new drugs into the firmly adherent mucus.

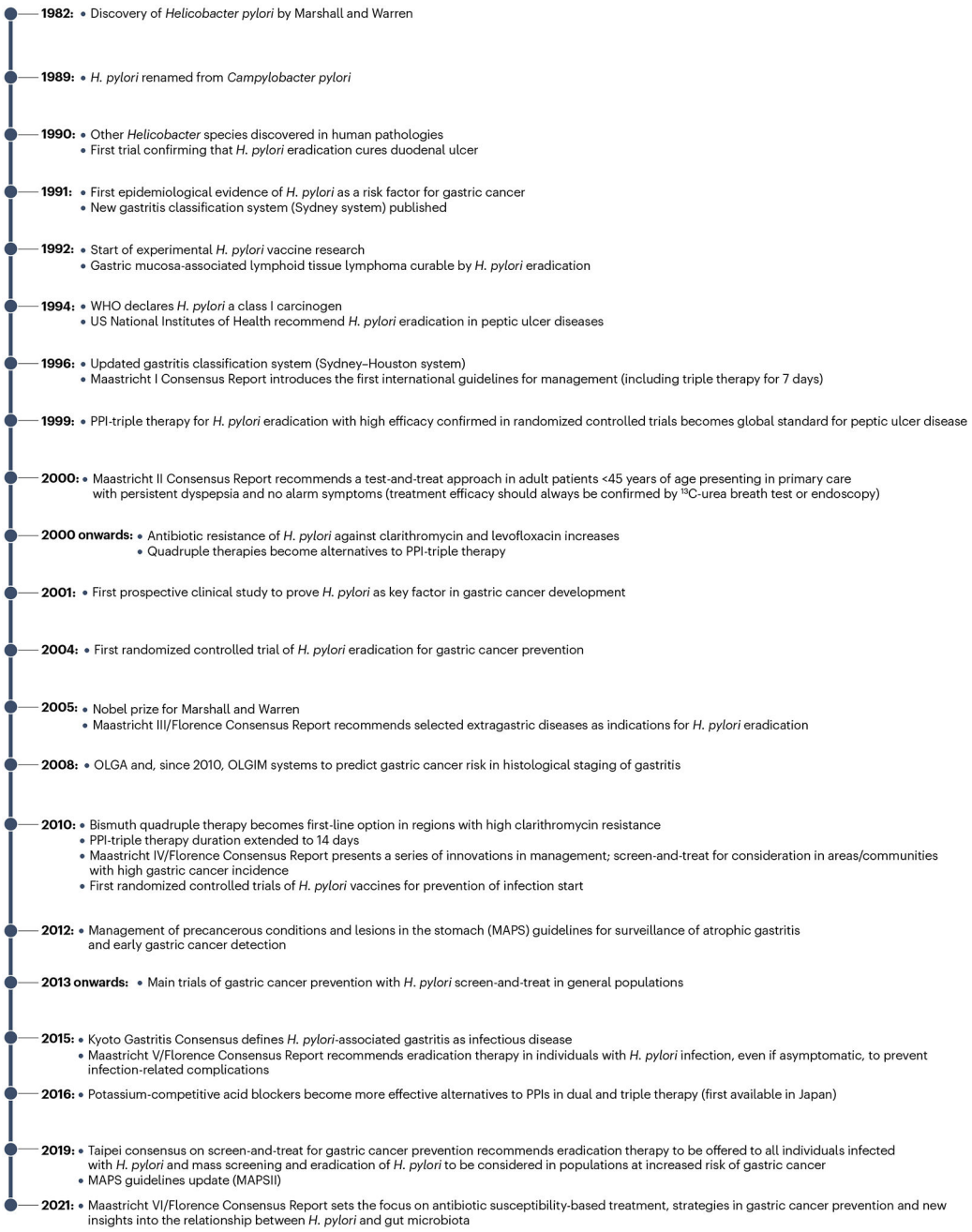

Fig. 1 |. Key developments in *H. pylori* clinical research and management.

Helicobacter pylori was discovered and reported at a conference in 1982 but the finding was not further disseminated before the first publication in 1983 (ref. 7). The timeline highlights key developments in clinical research of *H. pylori* infection and its therapeutic management since 1982 (refs. 1,10–12,14,15,17,21,70,184,224,241,311,336,377–383). OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastritis/Intestinal Metaplasia Assessment; PPI, proton pump inhibitor.

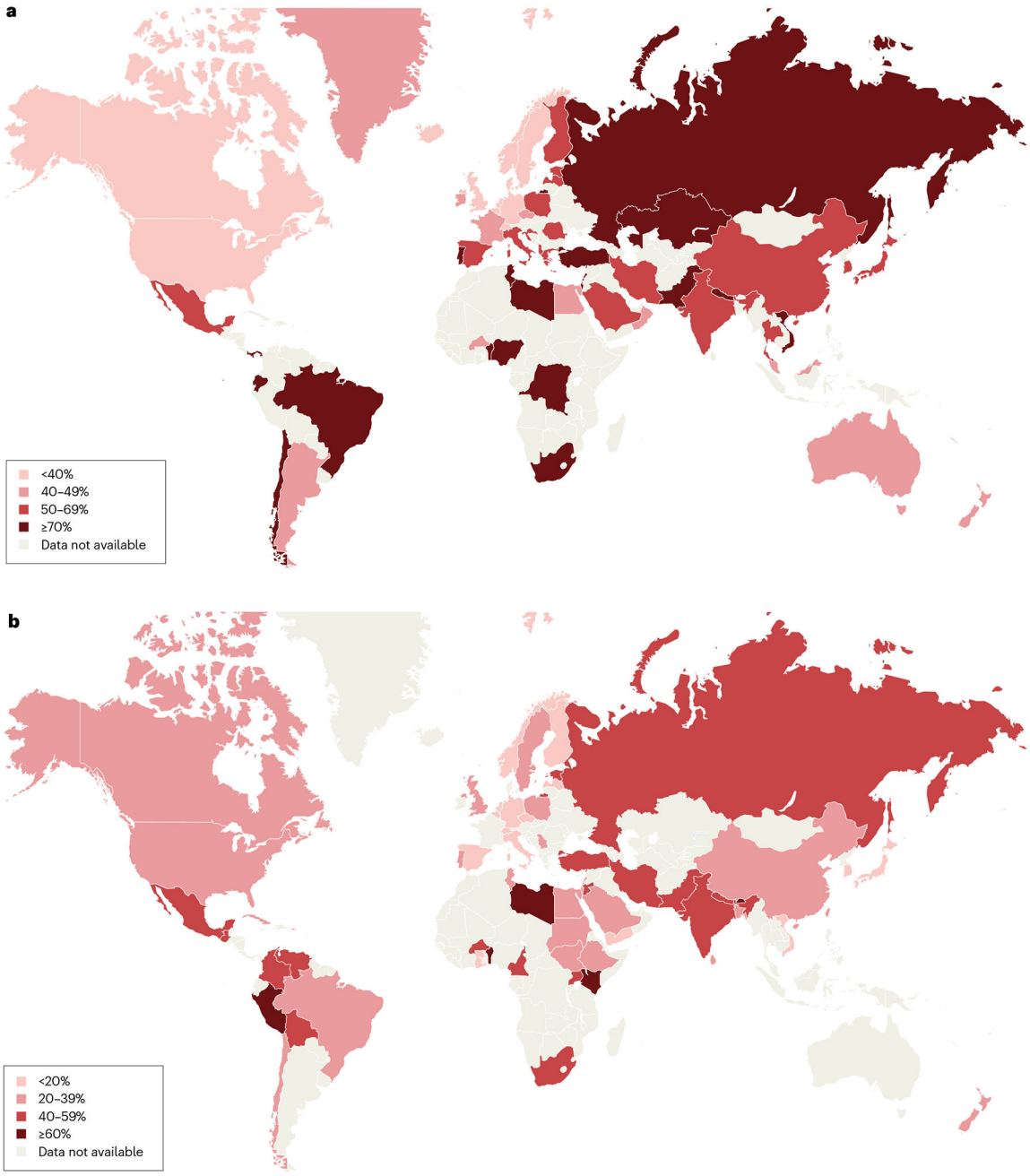

Fig. 2 |. Prevalence of *H. pylori* infection in adults and children.

a,**b**, Global map of *Helicobacter pylori* infection prevalence in adults during 1970–2016 (part **a**) and in children and adolescents (<20 years) during 2000–2021 (part **b**). In adults, the prevalence was highest in Africa, Eastern Mediterranean regions, Russia, Middle America and South America. In children, the prevalence was lower than that in adults in Russia, Western Pacific regions and European regions. However, the prevalence of *H. pylori* infection was similarly high in children and adults in Africa, Eastern Mediterranean regions, and Middle America and South America[16,24].

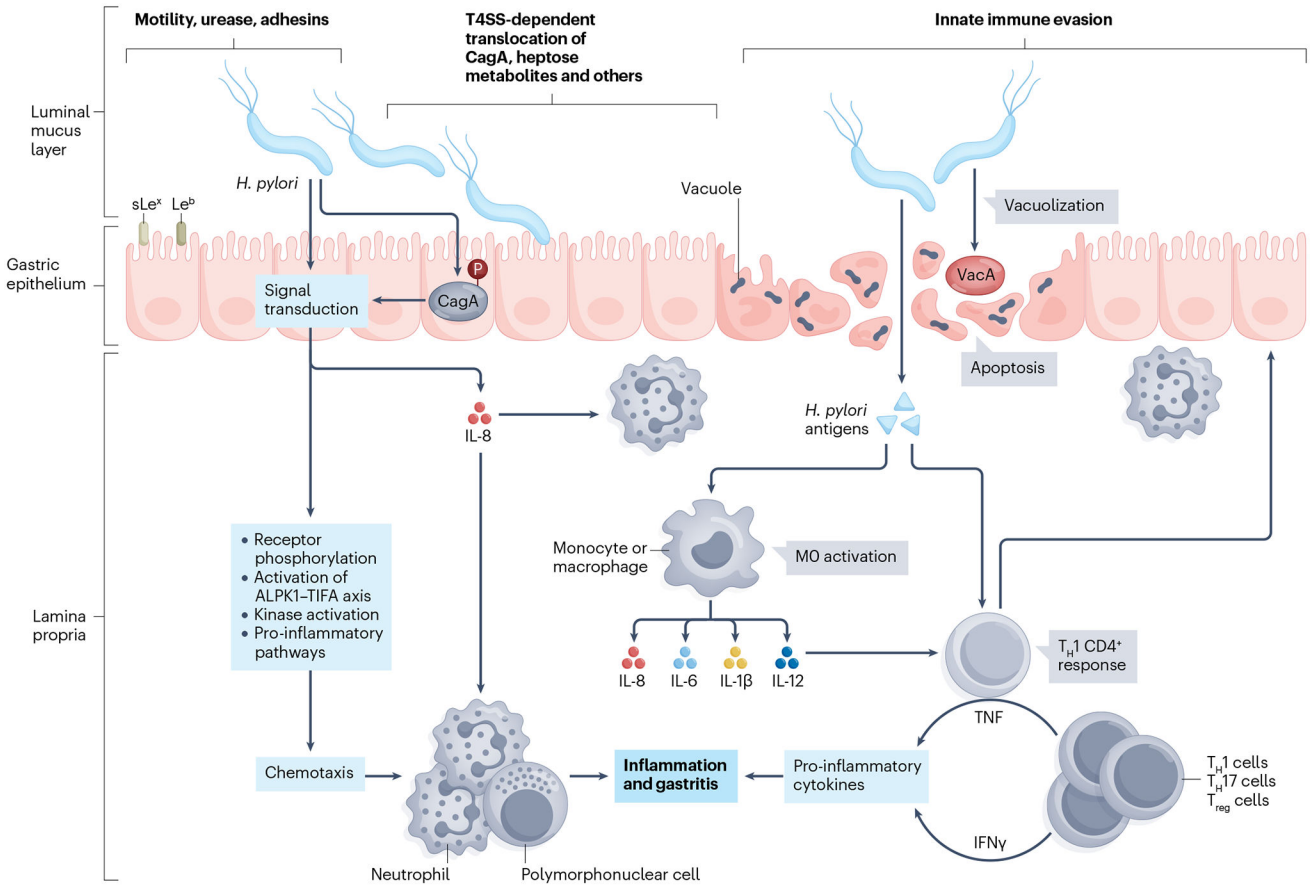

Fig. 3 |. *H. pylori* infection and pathogenesis.

Key aspects of bacterial colonization involve flagellar motility, urease activity, mechanisms of adhesion and damage to the gastric epithelium via vacuolization. The *Helicobacter pylori* pathogenicity island exerts a key role in inflammation, composes a type IV secretory system (T4SS) and promotes the intracellular injection of cytotoxin-associated gene A (CagA) antigen. The host immune response is characterized by initial mucosal invasion with polymorphonuclear cells followed by activation of the innate and adaptive immune system with complex T helper 1 (T_H1), T_H17 and regulatory T (T_{reg}) cell interactions. Le^b, Lewis b blood group antigen; sLe^x, sialyl-Lewis x antigen.

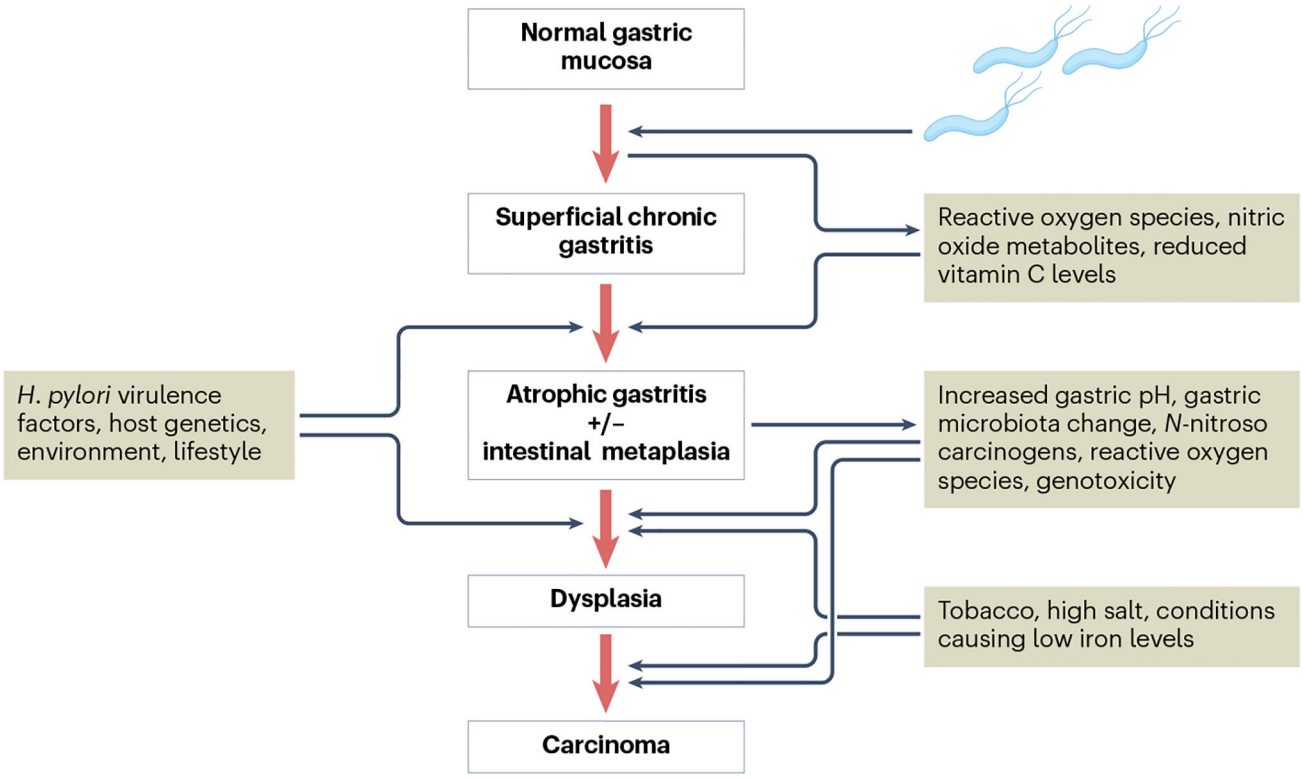

Fig. 4 |. Pathogenesis of gastric adenocarcinoma triggered by *H. pylori*.

The Correa cascade describes the dynamic progress of gastric carcinogenesis along the stepwise evolution of chronic gastritis initiated by *Helicobacter pylori* infection. *H. pylori* causes chronic gastritis that is associated with the generation of reactive oxygen species and nitric oxide metabolites and a reduction in antioxidant vitamin C levels. The risk of gastric cancer is highest in individuals who have infection by more virulent *H. pylori* strains, have pro-inflammatory host genetic factors, poor diet (high salt, smoked foods), low iron levels, unhealthy lifestyle and/or smoking habit. In these individuals, sustained chronic inflammation leads to damage and loss of acid-producing parietal cells, which leads to hypochlorhydria and finally achlorhydria. The loss of acidity facilitates colonization by harmful pro-inflammatory gastric microbiota, which in turn may produce more genotoxic pro-inflammatory metabolites and carcinogens that act directly on malignant epithelial cell transformation in the stomach[384–386].

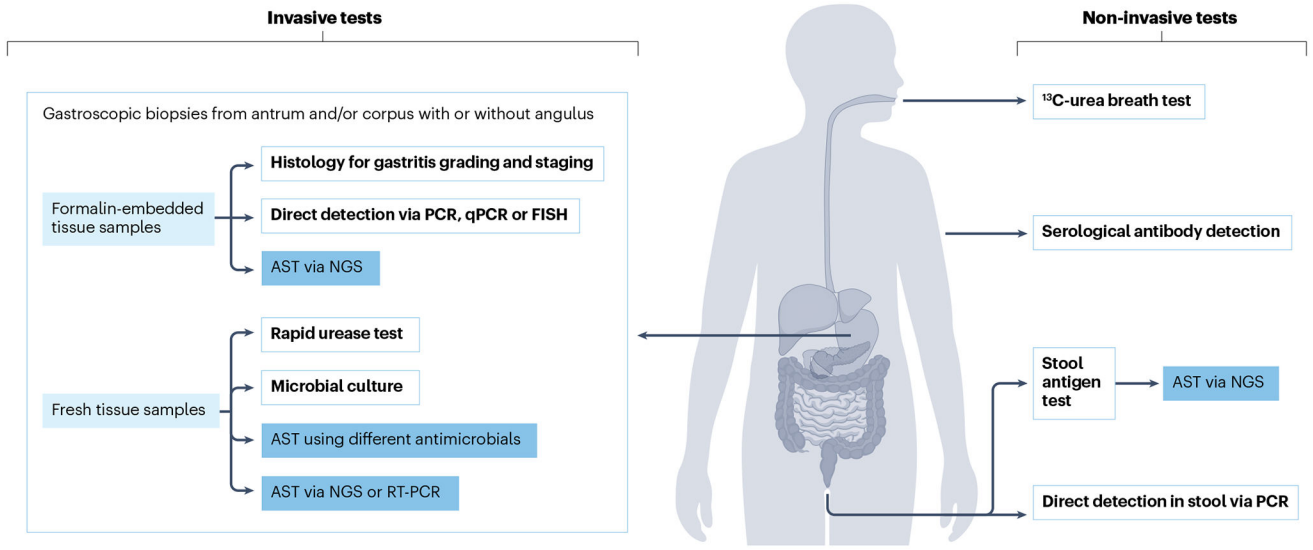

Fig. 5 |. *H. pylori* diagnostic procedures.

Diagnostic procedures are selected according to clinical scenarios. Non-invasive testing with the ^{13}C-urea breath test and stool antigen test enables diagnosis of a current infection. Serological *Helicobacter pylori* antibody detection does not enable differentiation between current and previous *H. pylori* infection, necessitating confirmation by ^{13}C-urea breath test or stool antigen test. All invasive tests are based on biopsy samples from gastroscopy. These enable histological assessment for gastritis grading and staging, direct *H. pylori* detection via PCR, microbial culture, rapid urease test, and molecular examinations. Antibiotic susceptibility testing (AST) can be performed from stool or biopsy samples using microbial culture, next-generation sequencing (NGS) or real-time PCR (RT-PCR) techniques. FISH, fluorescence in situ hybridization; qPCR, quantitative PCR.

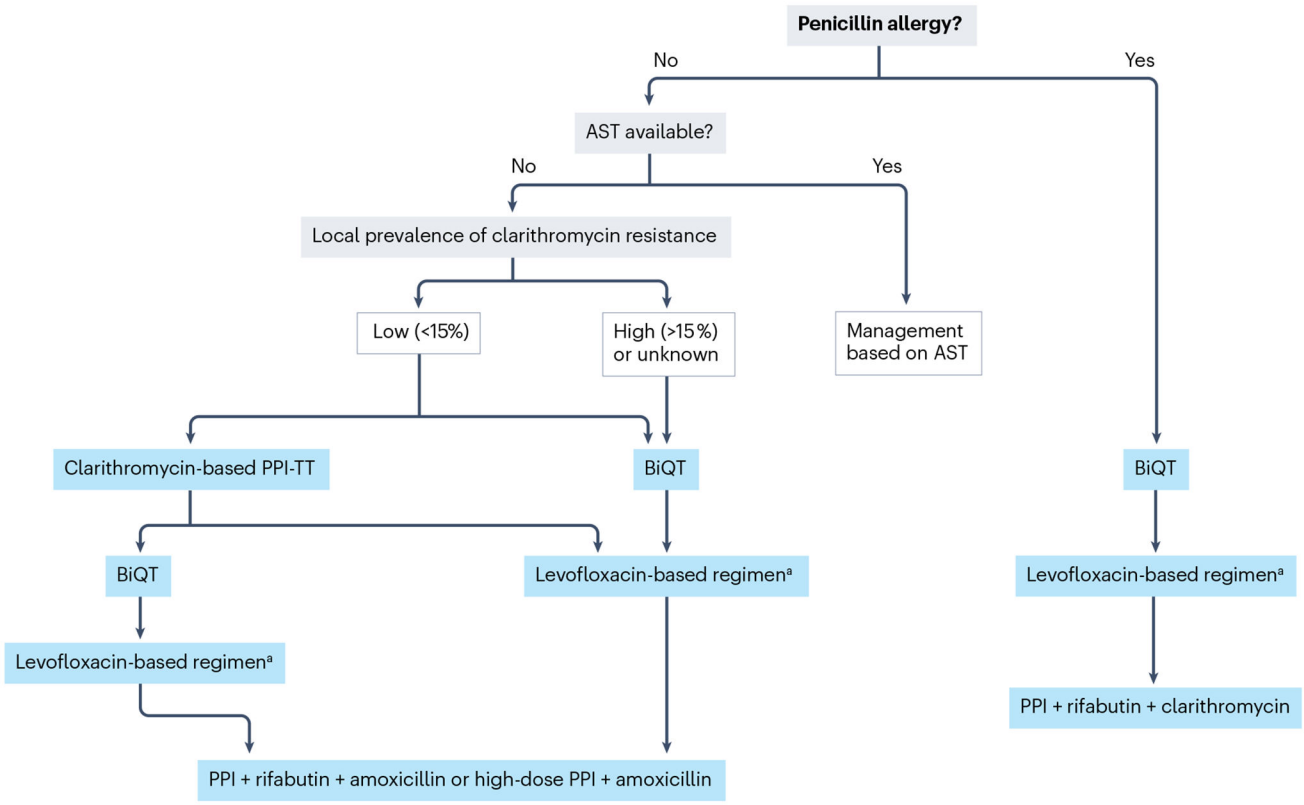

Fig. 6 |. Suggested *H. pylori* therapy algorithm.

Helicobacter pylori therapy algorithm with the indication of regimens that consist of triple or quadruple combinations to be used in first-line and subsequently in case of failure. Proton pump inhibitors (PPIs) or, where available, potassium-competitive acid blockers are essential components for acid suppression to render antibiotics more effective. PPI can be substituted by potassium-competitive acid blockers where available. Antibiotics are selected according to individual antibiotic susceptibility testing (AST) or according to regional antibiotic susceptibility based on surveillance as well as according to local availability. Clarithromycin-based PPI triple therapy (PPI-TT) is a first-line therapy if local clarithromycin resistance prevalence is <15%. If clarithromycin resistance exceeds 15% or is unknown, the recommended first-line regimen is BiQT (PPI, bismuth, tetracycline and a nitroimidazole antibiotic). Levofloxacin-based regimens are recommended as second-line treatments if a first-line regimen with BiQT fails. Levoflaxin-based regimens include amoxicillin and PPI. If levofloxacin resistance in regional surveillance exceeds 15%, it is advisable to directly select third-line or fourth-line regimens as rescue therapy. The fourth-line regimen (rescue therapy) consists of PPI, rifabutin and amoxicillin (or clarithromycin in case of penicillin allergy).

Table 1 |

Disease phenotypes of *H. pylori* infection

Phenotype	Frequency	Localization	Effect on secretory function	Possible outcomes[a]
Mild gastritis phenotype	Most patients	No specific gastric compartment predominantly affected	Normal acid secretion	Asymptomatic in most patients, no significant clinical outcome
Duodenal ulcer phenotype	10–15% of patients	Antral-predominant gastritis	High gastrin and acid secretion and impaired inhibitory control of acid secretion	Dyspeptic symptoms, duodenal ulcer
Gastric cancer phenotype	~1% of patients	Corpus-predominant gastritis	Low or absent acid secretion; variable gastrin secretion	Severe atrophic gastritis and intestinal metaplasia, gastric cancer

[a]Gastric ulcer and mucosa-associated lymphoid tissue lymphoma are not associated with a distinct gastritis phenotype. Gastric ulcer is associated more frequently with predominant corpus-type gastritis and low acid secretion. H. pylori, Helicobacter pylori.

Table 2 |

Indications for *H. pylori* testing

Indications for testing	Recommendation[a]		Refs.
	Strong	Weak	
Active or history of peptic ulcer disease	x		42,86
Low-grade gastric mucosa-associated lymphoid tissue lymphoma	x		86,337,338
History of endoscopic resection of early gastric cancer	x		86,219
Non-investigated dyspepsia in patients <50 years of age with no alarm symptoms	x		42,86
Investigated non-ulcer dyspepsia (functional dyspepsia)	x		42,86
First-degree relatives of patients with gastric cancer	x		42,86,214
First-generation immigrant from an area with high prevalence of *Helicobacter pylori* infection	x		42,86
Unexplained iron-deficiency anaemia when other causes have been excluded	x		42,86
Immune thrombocytopenia in adults	x		42,86
Long-term proton pump inhibitor use	x		42,86
Long-term acetylsalicylic acid and long-term NSAIDs, in consideration of individual additional risks		x	42,86,211

[a]Levels of recommendations are adapted and based on current international guidelines and consensus reports and selected randomized controlled trials[42,86].

Table 3 |

Diagnostic methods for *H. pylori* detection

Test	Sensitivity	Specificity	Clinical use	Comments	Refs.
Invasive methods					
Rapid urease test	84–95%	95–100%	Important for initial diagnosis; testing two biopsy samples improves sensitivity; provides rapid results	PPIs need to be stopped 14 days before testing; current or recent antibiotic therapy needs to be excluded	86,179
Microbial culture	76–90%	100%	Important for phenotypic susceptibility testing	Absolute specificity but costly; PPIs need to be stopped 14 days before testing; current or recent antibiotic therapy needs to be excluded	86,179
Histological assessment	60–93%	>95%	Gold standard for diagnosis and assessment of mucosal changes	Based on updated Sydney system	86,373
Molecular testing (PCR methods and FISH)	80–95%	100%	Useful in initial diagnosis and follow-up; provides rapid results	High sensitivity and specificity; useful in gastrointestinal bleeding, virulence typing and detection of antibiotic resistance	86,179,373–375
Non-invasive methods					
UBT	95–100%	95–100%	Gold standard for non-invasive diagnosis; higher sensitivity and specificity than stool antigen test and serological assessment; for initial diagnosis and follow-up	PPIs need to be stopped 14 days before testing; current or recent antibiotic therapy needs to be excluded	86,179,373
Stool antigen test	>95%	>95%	Useful for initial diagnosis and follow-up; slightly lower sensitivity than UBT	Rapid, simple and inexpensive	86,373
Serological antibody detection	74.4%	59%	Useful for initial diagnosis in specific cases	Cheap, simple and rapid; highly variable results; ideal for epidemiological purposes; no need to stop PPI and useful in patients with gastrointestinal bleeding; cannot distinguish between active and previous infection	86,179,376

FISH, fluorescence in situ hybridization; H. pylori, Helicobacter pylori; PPI, proton pump inhibitor; UBT, ^{13}C-urea breath test.

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