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ORIGINAL ARTICLE

Management of *Helicobacter pylori* infection: The Bhubaneswar Consensus Report of the Indian Society of Gastroenterology

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Abstract

The Indian Society of Gastroenterology (ISG) felt the need to organize a consensus on *Helicobacter pylori* (*H. pylori*) infection and to update the current management of *H. pylori* infection; hence, ISG constituted the ISG's Task Force on *Helicobacter pylori*. The Task Force on *H. pylori* undertook an exercise to produce consensus statements on *H. pylori* infection. Twenty-five experts from different parts of India, including gastroenterologists, pathologists, surgeons, epidemiologists, pediatricians, and microbiologists participated in the meeting. The participants were allocated to one of following sections for the meeting: Epidemiology of *H. pylori* infection in India and *H. pylori* associated conditions; diagnosis; treatment and retreatment; *H. pylori* and gastric cancer, and *H. pylori* prevention/public health. Each group reviewed all published literature on *H. pylori* infection with special reference to the Indian scenario and prepared appropriate statements on different aspects for voting and consensus development. This consensus, which was produced through a modified Delphi process including two rounds of face-to-face meetings, reflects our current understanding and recommendations for the diagnosis and management of *H. pylori* infection. These consensus should serve as a reference for not only guiding treatment of *H. pylori* infection but also to guide future research on the subject.

Keywords Antibiotic resistance · Duodenal ulcer · Gastritis · Gastric cancer · *Helicobacter pylori* eradication · Rescue therapies · Salvage therapy · Treatment failure · Treatment outcome

Introduction

Helicobacter pylori (*H. pylori*) is one of the common bacterial infections affecting humans globally. *H. pylori* infection is very important because of its association with various gastroduodenal diseases, especially peptic ulcer and gastric malignancies. The first Indian Consensus Conference on *H. pylori* was held in Mumbai on 22 and 23 February 1997, and a position paper was published in 1997 [1]. The 2nd National Workshop on *Helicobacter pylori* was organized at Thrissur, Kerala, on February 20, 1999, and the Recommendations for *Helicobacter pylori* management was published in 2000 [2]. However, in the last two decades, there has been considerable research on *H. pylori* infection and more data on *H. pylori* including information concerning the management of *H. pylori* infection have become available. Besides, a large number of updates on management guidelines and consensus statements from Asia Pacific region [3–5], Europe [6], and North America [7] have been published in the past few years. In view of the huge burden of *H. pylori* infection in India, the advances in management of the infection, and the differences in the etiological association between *H. pylori* and gastroduodenal diseases in India compared to other regions, it was felt that it was very important to develop Consensus on the management of *H. pylori* in India. Hence, the Indian Society of Gastroenterology (ISG) felt it was necessary to organize a third consensus on *H. pylori* infection in Indians to establish an updated consensus document on the current management of *H. pylori* infection and for this purpose constituted the ISG

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Task Force on *H. pylori*. The Task Force on *H. pylori* undertook an exercise to produce consensus statements on *H. pylori* infection in Indians.

Methods

The ISG Task Force on management of *H. pylori* infection was constituted with twenty-five experts from different parts of India, including gastroenterologists, pathologists, surgeons, epidemiologists, microbiologists, and pediatricians. They were invited to participate in the consensus development process on *H. pylori* infection in Indians to establish an updated document on the *H. pylori* infection. They were selected on the basis of their experience in *H. pylori* management or published literature in this field. It was decided to divide the Task Force into four groups to study the four major areas of *H. pylori* infection, and synthesize statements for consensus development after reviewing all pertinent literature on the subject. The groups were as follows: Epidemiology of *H. pylori* infection in India and the associated conditions; diagnosis; treatment and retreatment; *H. pylori* prevention/public health; and *H. pylori* and gastric cancer.

Each group reviewed all published literature on *H. pylori* infection with special reference to the Indian data and after thorough brainstorming prepared appropriate statements on various aspects of *H. pylori* infection for voting among the entire group for developing the consensus. This consensus was produced through a modified Delphi process including two rounds of face-to-face meetings at Bhubaneswar. The statements prepared by each group were submitted for a final consensus voting by all the participants. Eighty percent or higher votes were considered acceptance for the final statement. The statements were reviewed and voted for any of the five options based on the available evidences. The options given for each statement were (a) accept completely, (b) accept with some reservation, (c) accept with major reservation, (d) reject with reservation, and (e) reject completely. Consensus on a statement was considered to be achieved when 80% or more of the voting members chose to "accept completely" or "accept with some reservation" in favor of the statement. The statements were "rejected" if 80% of voting members voted for either *reject with reservation or reject completely*. Statements on important issues, which were not found to be acceptable were modified for a final round of voting if the voting members felt so. The modified statements were again subjected to voting for either acceptance or rejection. Subsequently, the relevant data were presented, and the level of evidence and strength of recommendation were graded using a modified protocol proposed by the Canadian Task Force on the Periodic Health Examination (Table 1) [8, 9]. The 1st Meeting of the Task Force was held in Bhubaneswar on 28 and 29 January, 2017. The statements for all sections except the statements in the section on "Treatment" were voted and finalized during the 1st Task Force Meeting in Bhubaneswar in 2017. During the Bhubaneswar Meeting, it was felt that the Statements on Treatment needed to be fine-tuned and re-voted to achieve a consensus. The group of experts on treatment after consultations finally drafted the revised statements on "Treatment" and subsequently all the statements including the "revised statements on treatment" were discussed and voted during the 2nd face to face Task Force Meeting in Bhubaneswar on 7 and 8 April 2018. Finally, the Task Force achieved a consensus on the following 39 statements on *H. pylori* infection in Indians.

Helicobacter pylori: epidemiology and associations

Statement 1: *Helicobacter pylori* infection is transmissible.

Level of evidence: II-2
Grade of recommendation: B
Agreement: 100%.

Helicobacter pylori is a spiral shaped Gram-negative bacterium. The transmissible nature of the infection is well established from self-ingestion experiments in human [10, 11]. The exact mode of transmission is unclear but feco-oral and oro-oral route appear to be likely [12]. A study from southern India showed an increased rate of infection among subjects drinking municipal water compared to those drinking boiled/filtered water [13]. Another study from northern India among twenty-five couples showed an infection rate of 83.3% when one partner was infected compared to 28.5% ($p<0.01$) when the index partner did not have the infection [14]. These and several other studies from other countries indicate the transmissible nature of *H. pylori* [12, 15].

Statement 2: The reported prevalence of *H. pylori* infection from India shows regional variation.

Level of evidence: II-2
Grade of recommendation: B
Agreement: 100%.

There are limited data from India on the prevalence of *H. pylori* in the community; most reports are hospital based. A community-based study among 80 asymptomatic individuals from Chandigarh in 2002 found the prevalence to be 56.7%. Data from control population from case-control studies may be an indirect way of gauging the rate of infection in asymptomatic individuals. Available hospital-based data show variations in the rates of infections at different centers (Tables 2, 3, and 4). These reports span from 1990s to 2017 and the method of *H. pylori* detection was not uniform across the studies. Keeping these limitations in mind, the rate of infection in controls has been near the range of 30% to 80%

Table 1 Grading of recommendations: quality of evidence and strength of recommendation

Level of evidence		Strength of recommendation	
Grade	Description	Grade	Description
I	Evidence obtained from at least one randomized controlled trial	A	There is good evidence to support the statement
II-1	Evidence from well-controlled trials without randomization	B	There is fair evidence to support the statement
II-2	Evidence from well-designed cohort or case-control study	C	There is poor evidence to support the statement
II-3	Evidence from comparison between time or place with or without intervention	D	There is fair evidence to refute the statement
III	Opinion of experienced authorities and expert committees	E	There is good evidence to refute the statement

Modified from the 1984 updated proposal of the Canadian Task Force on the Periodic Health Examination [8, 9]

except in one study in which it was 10% (Table 3). As there have been changes in the socioeconomic status of our population and currently there are efforts to improve the sanitation, past data may not reflect the current scenario. There is therefore a need to assess the current prevalence of *H. pylori* infection in the community to estimate the real [24–26] burden of infection.

Statement 3: *H. pylori* infection is associated with a wide spectrum of organic and functional disorders in a subset of individuals.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%.

There is sufficient evidence showing *H. pylori* as an etiological factor for peptic ulcer, gastric cancer (GC), and mucosa-associated lymphoid tissue (MALT) lymphoma. In addition, *H. pylori* has also been associated with dyspepsia [32, 33]. However, in *H. pylori* infection, symptoms do not occur in most infected individuals.

Case-control studies from India have found an increased rate of *H. pylori* infection in patients with dyspepsia in comparison with controls (Table 2) [24–26]. The rate of infection has been around 50% to 60% among patients with dyspepsia in the studies published from India in the last 6 to 7 years [16–23, 34]. However, an exception to this was the study from Ladakh where the infection rate was as high as 93% [19]. A meta-analysis of seventeen case-control studies reported an odds ratio (OR) of 2 (1.7–2.5) for *H. pylori* causing dyspepsia [32]. Besides, some *H. pylori* eradication trials in dyspepsia have also shown beneficial effects of eradication suggesting a role of this organism in causing symptoms [32].

Several case-control studies from different parts of India have unequivocally demonstrated a positive association between *H. pylori* and peptic ulcer disease (PUD) (Table 3) [18, 26–31, 35]. A meta-analysis by Huang et al. has also clearly demonstrated an increased risk of PUD with *H. pylori* infection [36].

The role of *H. pylori* in causing GC is well established [37, 38]. A recent Cochrane meta-analysis reported a significant

Table 2 Frequency of *H. pylori* infection in patients with dyspepsia from India

Study [reference]	Tests for diagnosis of *H. pylori*	*H. pylori* positivity (no.); %
Saxena et al., Lucknow [16]	RUT, culture, histology, PCR	NUD (241); 55.2%
Adlekha et al., Kerala [17]	RUT, histology	Dyspepsia (530) ;62%
Shukla et al., Lucknow [18]	RUT, culture, histology, PCR	NUD (120); 50%
Sharma et al., Ladakh [19]	Histology	Dyspepsia (59); 93%
Kolekar et al., Mumbai [20]	UBT	Resistant dyspepsia (261); 52%
Saha et al., Delhi [21]	Stool antigen	Dyspepsia (50); 60%
Satpathi et al., Odisha [22]	Serology, RUT, pathology	Dyspepsia (165); 58.8%
Dutta et al., Vellore [23]	RUT	Dyspepsia Overall (1000); 41.9% 15–30 years (303); 42.6% 31–50 years (350); 48.3% > 50 years (347); 34.9%

NUD non-ulcer dyspepsia, *RUT* rapid urease test, *UBT* urea breath test

Table 3 *H. pylori* and dyspepsia—case-control studies from India

Study [reference]	Test for diagnosis	*H. pylori* positivity (no.); %	*p*-value
Mukhopadhyay et al., Delhi [24]	Histology	NUD (50); 54% Controls (10); 10%	0.01
Gill et al., Mumbai [25]	RUT, Histology	Dyspepsia (526); 65% Controls (82);46%	0.001
Prasad et al., Vellore [26]	Histology	NUD (119); 71.4% Controls (30); 83.3%	0.25

NUD non-ulcer dyspepsia, *RUT* rapid urease test

protective action of *H. pylori* eradication on the future occurrence of GC [38]. Interestingly, several case-control studies from India have failed to demonstrate a greater risk of GC with *H. pylori* infection [39–41]. It is thought that by the time GC develops, the background gastric mucosa might become atrophic and unfavorable for colonization by *H. pylori* [42]. This may be why the outcome of the case-control studies might not truly reflect whether the bacteria were present in the patient before cancer developed. Chronic *H. pylori* infection also leads to gastric MALT lymphoma in a very small percentage of infected patients [43].

Statement 4: While there is association between functional dyspepsia and *H. pylori*, data to support eradication is insufficient from India.

Level of evidence: I

Grade of recommendation: B

Agreement: 85.8%.

Notwithstanding a positive association between of *H. pylori* and dyspepsia, data from two randomized controlled trials (RCTs) in India have shown conflicting results. The first study from Delhi published in 1999 included 62 non-ulcer dyspepsia (currently called functional dyspepsia) patients with *H. pylori* infection [44, 45]. In the *H. pylori* treated group, 81% responded to treatment, while in the control group, only 30% responded (p=0.0003). A more recent and larger trial published from Kashmir showed 43.7% response rate in the treatment group (n=217), which was not significantly different from the response rates in controls (n=195, 36.9% response rate, p=0.13) [45]. A meta-analysis of RCTs with dyspepsia, which favored *H. pylori* eradication, showed no noticeable benefit in most of the individual trials but when the data were pooled together, a positive benefit was noted [46]. Current evidence from India is insufficient to recommend eradication therapy in dyspepsia. Neither should endoscopy be performed for the sole purpose of diagnosing *H. pylori* infection in patients with functional dyspepsia. Large well-designed multicenter trials to evaluate the role of *H. pylori* eradication in functional dyspepsia are required from India to formulate evidence-based guidelines in our population.

Table 4 *H. pylori* and peptic ulcer disease—case-control studies from India

Study [reference]	*H. pylori* positivity (no.); %	*p*-value
Prasad et al., Vellore [26]	PUD (57); 89.5% Controls (30); 83.3%	0.5
Romshoo et al., Kashmir [27]	DU (46); 76.1% Controls (30); 33.3%	0.01
Jain et al., Delhi [28]	DU (16); 82.5% NUD (160); 50.6%	<0.001
Tovey et al., Multi-center India [29]	DU (148); 92% Controls (290); 77%	<0.001
Singh et al., Chandigarh (community-based study) [30]	PUD (13); 84.6% Controls (80);56.7%	0.1
Mhaskar et al., Pune [31]	PUD (190); 60% Controls (125); 45%	0.01
Shukla et al., Lucknow [18]	PUD (30);70% NUD (120); 50%	0.038

PUD peptic ulcer disease, *DU* duodenal ulcer, *NUD* non-ulcer dyspepsia

Statement 5: All patients with PUD, early gastric cancer, and MALT lymphoma should be tested for *H. pylori* infection and treated appropriately.

Level of evidence: I
Grade of recommendation: A
Agreement: 100%.

Since *H. pylori* is an etiological agent for PUD, eradication therapy is recommended. Results of meta-analysis highlight the beneficial effect of *H. pylori* eradication in duodenal ulcer healing and prevention of recurrence of both duodenal and gastric ulcer [47]. Follow-up studies from southern India in patients with complicated (perforated) duodenal ulcers have demonstrated a beneficial effect of *H. pylori* eradication in preventing ulcer recurrence [48, 49]. All patients with PUD, with or without complications should be tested for presence of *H. pylori* infection, and if present, *H. pylori* should be eradicated. Similarly, in view of the recognized role of *H. pylori* in GC and MALT lymphoma (low-grade), testing for the infection and its therapy is recommended [38, 43].

Gastroesophageal reflux disease (GERD) and *H. pylori* The relationship between *H. pylori* infection and GERD remains controversial. This is largely because of ethnic and regional differences in the prevalence of *H. pylori* and GERD [6, 50, 51].

Statement 6: There is an inverse association reported between the prevalence of *H. pylori* and GERD.

Level of evidence: IIB
Grade of recommendation: A
Agreement: 100%.

The precise role played by *H. pylori* in the etiopathogenesis of GERD is contentious. The prevalence of GERD varies with site of localization of *H. pylori* colonization in the gastric mucosa. When *H. pylori* colonizes the antrum in the duodenal ulcer patients, the antral predominant gastritis causes enhanced acid production, and this predisposes to GERD. Following *H. pylori* eradication, there is normalization of acid secretion. On the other hand, *H. pylori* colonizes in the gastric corpus, i.e. pangastritis phenotype, there is reduced acid production and this offers protection against GERD. In this situation, following eradication, there is rebound acid secretion with worsening of GERD, except in situations when there is an irreversible atrophic gastritis. Thus, there is an inverse paradoxical relationship of GERD to the site of colonization of *H. pylori* and its eradication [52].

Proponents for protective role of *H. pylori* against GERD There are regional differences in the reported prevalence of GERD from the West and the Asian countries, with higher prevalence rates being reported from western countries like USA, Canada, Britain, and Scandinavian countries compared to lower frequency in Far East. Among the Asian countries, prevalence is higher in Japan compared to Korea, Singapore, and Hong Kong [42]. In India, the prevalence of GERD in the community is estimated to be 7.6% [9].

H. pylori prevalence is relatively low (30% to 50%) in the West (America, Europe, and Australia) and Japan compared to Eastern European, South American, African, and Asian countries (60% to 80%). In India, *H. pylori* prevalence ranges from 31% to 84% with a frequency of approximately 60% reported from most parts of the country [53]. Unlike the West, which has a high prevalence of not only GERD (10% to 20%), but also Barrett's esophagus and esophageal adenocarcinoma, the prevalence of GERD and its related complications in Asian countries is comparatively low (3%). Thus, the inverse relationship between *H. pylori* prevalence and occurrence of GERD and related disorders suggest a protective role of *H. pylori* against GERD.

Nam et al. enrolled 10,102 GERD patients, of whom 4007 were followed up for a median period of 2 years to compare the prevalence of reflux esophagitis and reflux symptoms between those in whom *H. pylori* was eradicated and those with persistence of infection [54]. While the overall prevalence of reflux esophagitis (by Los Angeles classification) was 4.9%, the prevalence was 6.4% in subjects without *H. pylori* infection, but 3.3% in those with *H. pylori* infection ($p< 0.001$). On multivariate analysis, *H. pylori* infection was found to exert a strong inverse association with reflux esophagitis (OR 0.42; 95% CI, 0.34–0.51).

Table 5 summarizes the various studies that address the relationship between *H. pylori* and GERD [55–60]. In a review of GERD in Asia, Goh highlighted the inverse relationship between GERD and *H. pylori* prevalence, and the apparent protection offered especially by the virulent strains of *H. pylori* [61]. Ghoshal and Chourasia have suggested that the occurrence of GERD following *H. pylori* eradication might be related to increase in the acidity of the esophageal refluxate and the presence of pre-existing abnormalities in gastroesophageal motility [62].

Factors other than *H. pylori* that might contribute to high prevalence of erosive esophagitis in the West may include metabolic syndrome and visceral obesity [63, 64]. Gunji et al., in a cross-sectional study of 9840 Japanese men, observed that higher body mass index (BMI) and triglycerides were predictors of an increased prevalence of erosive esophagitis (OR = 1.063 and 1.001; 95% CI = 1.020–1.108 and 1.001–1.002, $p = 0.004$ and $p <0.001$, respectively), while *H. pylori* infection independently decreased the prevalence of erosive esophagitis (OR = 0.346, 95% CI = 0.299–0.401, $p < .001$) [56].

A few studies have also shown an increase in body weight after eradication of *H. pylori*, which could also increase the

Table 5 Studies showing a negative association between *H. pylori* and erosive Esophagitis and Barrett's Esophagus in the West and East Asian countries

Study [references]	Type of study	Number of cases (*n*)	Diagnosis of *H. pylori*	*H. pylori* prevalence (%)
Chung et al., Korea [55]	Case-control	Reflux esophagitis (2,808) Control (2,808)	Serology	38.4 vs. 58.2
Gunji et al., Japan [56]	Cross-sectional	Erosive esophagitis (1,831) No erosive esophagitis (8,009)	Serology	13.6 vs. 33.4
Chiba et al., Japan [57]	Cross-sectional	Erosive esophagitis (728) No erosive esophagitis (4,262)	Serology	9.4 vs. 14.9
Ashktorab et al., USA [58]	Case-control	Reflux esophagitis (58) Gastritis (1,558) Reflux esophagitis + gastritis (363) Normal control (41)	Biopsy silver stain or immunohistochemistry	3.8 vs. 40 vs. 34 vs. 34
Sonnenberg et al., USA [59]	Cross-sectional	Barrett's esophagus (2,510) No Barrett's esophagus (76,475)	Biopsy immunohistochemistry	5.7 vs. 12.2
Thrift et al., Australia [60]	Case-control	Barrett's esophagus (217) Dysplastic BE (95) Control (398)	Serology	12 vs. 3 vs. 18

risk for development of GERD [65]. A randomized controlled trial in the UK, in which *H. pylori*–infected patients were randomized to eradication therapy vs. placebo, observed that more subjects in the intervention group gained >3 kg body weight compared to the placebo group (OR 1.57, [95% CI: 1.17, 2.12]) [65]. The authors suspected that the gain in body weight could have been due to reduction in dyspeptic symptoms.

Proponents for a positive association between *H. pylori* and GERD Wu et al. reported that eradicating *H. pylori* increased esophageal acid exposure and in some cases worsened reflux symptoms [66]. Besides, Chen and Chang also did not find a negative association between *H. pylori* and GERD [67]. At the same time, Yarandi et al. too observed a positive association of *H. pylori* with GERD [67, 68]. The authors concluded that *H. pylori* infection was more common in patients with than those without GERD.

In summary, studies from the West reveal conflicting data on the association between *H. pylori* and GERD [69–73]; on the contrary, studies from the East especially Asia clearly reveal a negative association between *H. pylori* and reflux esophagitis [57, 74–76].

Statement 7: *H. pylori* eradication does not cause GERD.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%.

A post-hoc analysis of 8 RCTs by Laine and Sugg showed no significant difference in the new onset erosive esophagitis or GERD symptoms between those with successful and those with failed *H. pylori* eradication among patients with duodenal ulcer and GERD [77]. Among patients with pre-existing GERD, there was symptomatic aggravation in 7% of those who had eradicated infection and in 15% of those with persistent infection (OR=0.47; 95% CI 0.24–0.91; p =0.02). The new onset of GERD or aggravation of GERD symptoms may be due to corpus predominant gastritis developing following *H. pylori* eradication with restitution of parietal cell mass and increased gastric acid secretion.

However, a few studies have shown no new-onset gastroesophageal reflux (GER), or worsening of existing GER symptoms. The United Kingdom, Bristol Helicobacter Project showed that neither was treatment for *H. pylori* infection associated with an increase in prevalence of heartburn and other reflux symptoms, nor was there any improvement in reflux symptoms in patients with pre-existing symptoms [78]. In a systematic review on the effect of *H. pylori* eradication on GERD symptoms in patients with either duodenal ulcer (DU) or esophagitis, Raghunath et al. did not find any predisposition to development of new onset of GERD or worsening of existing symptoms [79]. Besides, three RCTs

too found no influence of eradication of *H. pylori* on healing rates or symptomatic response in patients with erosive esophagitis [80–82]. The Maastricht IV Consensus Report too concluded that *H. pylori* eradication did not worsen pre-existing GERD or influence response to therapy. Although a large cohort study from Korea initially showed inconsistent results, the revised Korean guidelines also reiterate that eradication of *H. pylori* did not affect the development or clinical course of GERD [5, 83].

Nam et al. reported an increase in reflux esophagitis after successful eradication of *H. pylori* infection (OR 2.34; 95% CI, 1.45–3.76; $p < 0.001$) which was comparable to the *H. pylori*–negative group (OR 2.42; 95% CI, 1.73–3.36; $p < 0.001$) [54]. The reflux symptoms had no relationship with *H. pylori* infection or eradication. On the other hand, Xie et al. in a meta-analysis of 4 Asian RCTs concluded that *H. pylori* eradication could be a factor for *de novo* endoscopic GERD, especially in Asian populations [84]. Table 6 shows the meta-analyses of 4 studies [84–87].

Statement 8: In patients with GERD, routine testing for *H. pylori* infection and its treatment are not recommended.

Level of evidence: I

Grade of recommendation: B

Agreement: 100%.

As per the American College of Gastroenterology (ACG) guidelines, and based on available evidence, in a patient with typical GERD symptoms, testing for *H. pylori* infection is not necessary, except in patients with history of PUD and dyspepsia. Patients with GERD who are *H. pylori* positive may be treated for *H. pylori*, but acknowledging the fact that GERD symptoms are unlikely to improve following eradication. Most European and Asia Pacific regions have nonerosive reflux disease and *H. pylori* infection is common [88]. Some response in GERD symptoms is likely in patients treated with proton pump inhibitors (PPI) or *H. pylori* eradication followed by PPI as sequential therapy, especially when associated with dyspepsia or duodenal ulcer.

In patients with erosive esophagitis, PPI is the first-line treatment for control of symptoms. *H. pylori* eradication in these patients is more for reduction of long-term complications. In symptomatic GERD, endoscopy is often not indicated, and treatment is as for nonerosive reflux disease (NERD). Some response to symptoms may exist (40%) in coexisting dyspepsia [89]. As most studies show no benefit from *H. pylori* eradication with respect to reflux symptoms or endoscopic severity, routine testing for *H. pylori* and treating the infection are not recommended.

Statement 9: *H. pylori* testing and treating it if detected are recommended in patients who are on long-term PPI as maintenance therapy for GERD.

Level of evidence: III

Grade of recommendation: C

Agreement: 86.9%.

There are apprehensions that prolonged treatment with PPIs in *H. pylori*–infected patients might increase the susceptibility for developing gastric cancer [90, 91]. Currently, there is ambiguity on the issue of eradicating *H. pylori* infection in patients with GERD [92]. From the Indian perspective, there is no data on this contentious issue.

In *H. pylori*–infected patients, long-term PPI for GERD may even worsen the histological severity of gastritis. This could further accelerate the development of gastric mucosal atrophy. However, adenocarcinoma has generally not been reported when PPI is introduced in patients sans infection or after an initial eradication therapy [93, 94]. Nevertheless, in younger patients, there is need for eradication of *H. pylori* before commencement of long-term PPI therapy, although long-term data that address progression of gastric atrophy to carcinoma are lacking [95]. Hence, the decision for treating *H. pylori* has to be made on a case to case basis, considering all the relevant variables including cost benefit, less need for PPI, and reduction of severity [96].

Both ACG guidelines and Maastricht III/IV Consensus Report published guidelines for *H. pylori* testing. The former recommends definitive treatment for patients with current as well as past gastric and duodenal ulcer, gastric MALT lymphoma, patients who have undergone endoscopic resection of early gastric cancer, and uninvestigated dyspepsia. However, the latter advises treatment in individuals with history of gastric cancer in a first-degree relative, atrophic gastritis, unexplained iron-deficiency anemia, chronic idiopathic thrombocytopenic purpura, and individuals with history of PUD prior to starting non-steroidal anti-inflammatory drugs (NSAIDs) in addition. As prophylaxis, it is recommended in patients with history of PUD who are taking aspirin or have unexplained vitamin B_{12} deficiency. Both these guidelines do not mention the need for eradication of *H. pylori* in a setting of long-term PPI in GERD patients. However, the Asia-Pacific consensus recommendations for *H. pylori* infection advocate *H. pylori* eradication in GERD patients who are on long-term PPIs [3]. Till date, however, there is no evidence that *H. pylori* eradication reduces the risk of gastric adenocarcinoma.

In Asian countries, there is a negative association between the frequency of *H. pylori* infection and the prevalence and severity of GERD [97]. It has been observed in patients with a combination of DU and GERD that *H. pylori* eradication does not worsen GERD. In fact *H. pylori* infection may be protective against GERD [98]. Besides, Barrett's esophagus (BE) is also more common in individuals who do not harbor *H. pylori* infection, and the risk of esophageal adenocarcinoma with BE

Table 6 Meta-analysis of randomized controlled trials

Study [references]	Number of enrolled studies	Location of enrolled studies	Risk ratio (95% confidence interval)	Conclusion
Xie et al. [84]	Cohort studies: 12 RCTs: 12	*Cohort* Europe:4 USA:1 Asia:7 *RCTs* Europe:7 S America:1 Asia: 4	**Type A cohort studies: 3** 2.50 (1.46–4.26,*p*=0.0008) **Type B cohort studies: 9** 1.70 (1.30–2.23, $p = 0.0001$) **RCTs: 12** 1.09 (1.23–3.22, $p = 0.005$) **Asian RCTs: 4** 4.53 (1.66–12.36, $p = 0.003$)	Eradication of *H. pylori* may be a risk factor for *de novo* endoscopic GERD, especially in Asian populations
Yaghoobi et al. [85]	Cohort studies: 5 RCTs: 7	*Cohort* Europe:1 Asia:4 *RCTs* Europe:3 USA:3 S America: 1	**Cohort studies: 5** 1.37 (0.89–2.12, $p = 0.15$) **RCTs: 6; *outcome: EE*** 1.11 (0.81–1.53, $p = 0.52$) **RCTs**: 5; ***outcome: symptomatic GERD*** 1.22 (0.89–1.69, $p = 0.22$)	No association between *H. pylori* eradication and new onset GERD in dyspeptic patients.
Qian et al. [86]	RCTs: 11	Europe:5 USA:3 S America:1 Asia:1 Multinational: 1	**RCTs: 7** outcome: heartburn 0.88 (0.63–1.23, $p = 0.46$) **RCTs: 10**: outcome EE 0.97 (0.67–1.40, $p = 0.88$)	*H. pylori* eradication does not aggravate clinical outcomes: short-term and long-term post eradication occurrence of GERD
Saad et al. [87]	RCTs :10	Europe:7 USA:2 Asia: 1	**RCTs: 10;** ***Outcome: symptomatic GERD*** 0.81 (0.56–1.71, $p = 0.27$) **RCTs: 10;** ***Outcome:*** ***endoscopic esophagitis*** 1.13 (0.72–1.78, $p = 0.59$)	*H. pylori* treatment does not seem to increase GERD symptoms or reflux esophagitis. Eradication, seems to significantly improve GERD symptoms

RCTs randomized controlled triala, *GERD* gastroesophageal reflux disease, *EE* endoscopic esophagitis

is also less in persons with *H. pylori* infection [99]. Long-term maintenance treatment with PPI in GERD patients with *H. pylori* induces corpus predominant atrophic gastritis, reduced acid secretion, and therefore is more likely to be protective against GERD and its complication like adenocarcinoma [100]. These are often seen with cytotoxin-associated gene A (cag-A) positive strains [101]. Similar observations have been made in Africa [102]. Based on these observations, and also in the absence of conclusive supporting evidence, currently there is no indication for eradication of *H. pylori* in GERD patients who require long-term PPI.

Based on the current evidence, patients with typical GERD symptoms should not be tested for *H. pylori* infection, unless there is associated dyspepsia symptoms or history of PUD. Besides, in case these individuals are offered treatment for *H. pylori* infection, they should be informed that GERD symptoms are not likely to improve.

Statement 10: Testing for *H. pylori* and treating it if detected is recommended in patients likely to be on or already on long-term NSAIDs/aspirin.

Level of evidence: I

Grade of recommendation: A

Agreement: 91.7%.

Both *H. pylori* and NSAIDs are known risk factors for PUD. Besides, a meta-analysis has shown that both factors, when present together, increased the risk of PUD much more than when present alone (OR 61.1, 9.98–373) [36]. The risk of bleeding from peptic ulcer also increases about 6-fold in patients taking NSAID if *H. pylori* infection is present [36]. In this context, there are two scenarios which are encountered in clinical practice. Firstly, in *H. pylori*–infected patients who have not received NSAID previously, there is favorable effect of *H. pylori* eradication in curtailing risk of development of peptic ulcer [103]. Secondly, in those who are already on NSAID, the risk of PUD does not decrease significantly after eradication [103]. In patients who have had PUD in past with or without complications like bleeding, and require NSAIDs, there is beneficial effect of treating *H. pylori* infection, but this alone may not suffice in preventing recurrent ulcer or its complications, and secondary prophylaxis with PPI is recommended as long as NSAID/aspirin is continued [104, 105].

Statement 11: Other indications for testing and treating *H. pylori* are idiopathic thrombocytopenic purpura (ITP), unexplained iron-deficiency, and vitamin B_{12} deficiency–related anemia.

Level of evidence: II

Grade of recommendation: B

Agreement: 91.7%.

H. pylori infection has also been associated with several extra-gastric conditions [106]. In a small minority, the infection may be linked to iron deficiency anemia as shown by a meta-analysis and eradication may be beneficial [107]. A couple of studies from India on *H. pylori* infection and anemia have demonstrated that response to iron supplements is better when the organism is eradicated [108, 109]. *H. pylori* eradication may have a beneficial effect in some patients with ITP and testing for *H. pylori* is recommended. This is also supported by a meta-analysis [110]. Besides, a study from southern India has also demonstrated the positive effect of *H. pylori* eradication in improving platelet counts in patients with chronic ITP [111]. Furthermore, there are also reports of vitamin B_{12} deficiency in association with *H. pylori* infection although the data on this appear to be conflicting [112–114].

Statement 12: Children with epigastric or upper abdominal pain, and with endoscopic findings of PUD (gastric or duodenal), should be tested and treated for *H. pylori*. Children with recurrent abdominal pain suggestive of functional pain should not be tested or treated for *H. pylori*.

Level of evidence: 1

Grade of recommendation: B

Agreement: 86.4%.

Chronic abdominal pain (CAP)/recurrent abdominal pain (RAP) is a common problem seen in 10% to 15% of children worldwide of whom 80% to 85% have functional abdominal pain. The association between RAP and *H. pylori* is debatable. Studies from Indian and abroad revealed that there is no significant difference in the prevalence of *H. pylori* infection between RAP and controls [115–117]. A study on 945 children from Germany and 695 children from Sweden [5] has shown that there is no association between presence of *H. pylori* infection and the occurrence of abdominal pain in children. A few other studies revealed there was an inverse relationship between *H. pylori* infection and abdominal pain [118, 119]. To conclude, *H. pylori* infection in children is mostly asymptomatic. A recent meta-analysis of 38 studies has failed to establish an association between RAP and *H. pylori* infection [120].

Interventional studies do not support an association of abdominal pain and *H. pylori* infection. Ashorn et al. conducted a double-blind randomized placebo-controlled trial of *H. pylori* eradication in 20 children with RAP. They clearly showed that *H. pylori* eradication and accompanying healing of gastric inflammation did not improve from abdominal pain [121]. However, a prospective study from India on 240 children documented higher *H. pylori* positivity (53.4%) among those with upper abdominal pain compared to those who did not present with upper abdominal pain (28%; p=<0.001)

[122]. Furthermore, anti-*H. pylori* treatment resulted in symptom free period of 25 months.

Based on the data available from published studies, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) have published guidelines for *H. pylori* infection in children in which they stated that there is lack of robust evidence to support a causal link between *H. pylori* gastritis and abdominal symptoms in the absence of peptic ulcer [123]. Hence, testing for *H. pylori* infection cannot be recommended for evaluation of children with functional abdominal pain. Only children with severe abdominal symptoms should be investigated primarily to exclude organic diseases, and not merely to detect *H. pylori* infection. Endoscopy is thus the preferred modality of investigation (invasive tests); non-invasive tests do not have a role in the initial evaluation. The recent Joint ESPGHAN/NASPGHAN guidelines for *H. pylori* have recommended that testing for *H. pylori* should only be performed in children with gastric or duodenal ulcer [124]. If *H. pylori* infection is detected, then treatment should be instituted followed by confirmation of *H. pylori* eradication. Thus, to conclude, there is inadequate evidence in favor of a "test and treat" approach for *H. pylori* infection in children.

Helicobacter pylori: diagnosis

Statement 13: Non-invasive tests (urea breath and stool antigen tests) are appropriate to confirm *H. pylori* eradication.

Level of evidence: II-2

Grade of recommendation: B

Agreement: 93.4%.

Non-invasive tests for *H. pylori* include urea breath test (UBT), serology, and stool antigen tests. Among these, ^{13}C UBT has highest sensitivity, specificity, and excellent performance [125, 126]. The ^{14}C UBT has also shown similar degree of sensitivity, specificity, and accuracy for diagnosis of *H. pylori*; however, due to radiation exposure and limited availability, it is less often used [125].

Stool antigen test is also an important modality for diagnosis of *H. pylori* in patients with dyspepsia. The sensitivity, specificity, and accuracy of stool antigen test has been found to be more than 95% and comparable to UBT [21, 127, 128].

Statement 14: Serological tests have no role in *H. pylori* management.

Level of evidence: II-2

Grade of recommendation: A

Agreement: 100%.

Serological tests based on immunoglobulin G (IgG) and immunoglobulin A (IgA), have been developed for the diagnosis of *H. pylori* infection [129]. These are least affected by prior exposure to antibiotics or PPI compared to other tests [130]. However, due to variability in host genetics, different *H. pylori* strains produce different levels of antibodies with variable sensitivity and specificity [125]. Moreover, a major drawback with these tests is that it cannot differentiate between active infection and remote infection. Hence, at present, only validated serological tests may be used for diagnosis of *H. pylori* especially for epidemiological purposes.

Statement 15: Before testing for *H. pylori* infection, PPI and antibiotics should be discontinued for at least 2 weeks as these may lead to false negative results

Level of evidence: II-2

Grade of recommendation: B

Agreement: 100%.

PPIs have been shown to possess anti-*H. pylori* activity and these decrease *H. pylori* load causing false negative rapid urease test (RUT) or stool antigen tests. Fourteen days interval is recommended before these diagnostic tests of *H. pylori* [131]. However, histamine-2 receptor blockers (H_2 blockers) have least effect on *H. pylori* and they are not suspected to affect the efficacy of UBT or stool antigen test [132].

Antibiotics or bismuth-containing compounds also decrease *H. pylori* load and cause false negative urease tests or stool antigen test. Antibiotic- or bismuth-containing compounds are recommended to be withdrawn for 4 weeks before these tests [125].

Statement 16: In clinical practice, if upper gastrointestinal (GI) endoscopy is indicated, RUT should be the first-line diagnostic test for detecting *H. pylori* infection. For the purpose of RUT, at least two biopsy samples should be taken—one from the corpus and another from the antrum.

Level of evidence: II-2

Grade of recommendation: Grade A

Agreement: 100%.

The RUT has shown sensitivity and specificity of more than 95% in diagnosis of *H. pylori*. False negative RUT results may occur if there is recent GI bleed, recent use of antibiotics or PPI, or excessive gastric atrophy [125]. However, ease of

usage and rapidity of result of RUT makes it an ideal diagnostic test of choice in patient undergoing upper GI endoscopy.

For RUT, acquiring tissue from both the antrum and fundus increases the sensitivity of the test [133]. Seth et al. have shown that only antral biopsy is associated with decreased sensitivity of RUT [134].

Statement 17: In clinical practice, during endoscopy, additional biopsy may be taken from corpus and antrum for histopathology.

Level of evidence: II-2

Grade of recommendation: Grade B

Agreement: 100%.

In clinical practice, it is also essential to know about the presence and degree of gastric atrophy and intestinal metaplasia due to *H. pylori*. These changes are seen more often over lesser curvature than greater curvature. Moreover, presence of these lesions in antrum can be due to multiple causes; however, gastric atrophy or intestinal metaplasia in corpus mucosa is generally a result of ongoing or cured *H. pylori* infection. As per the updated Sydney protocol, biopsies should be obtained from lesser and greater curvatures, and also from body and antrum [135]. However, studies have also shown that lesser and greater curvature of antrum, lesser and greater curvature of mid body, and angulus are the most appropriate sites for detection of *H. pylori* and gastric atrophy [136]. The presence of *H. pylori* at these sites also show concordance with the result of RUT tests and diagnosis of gastric atrophy according to updated Sydney classification system.

Statement 18: If there is a failure of second-line therapy and endoscopy is contemplated, culture for *H. pylori* along with standard antimicrobial testing are recommended.

Level of evidence: II-2

Grade of recommendation: B

Agreement: 93.4%.

After the second-line therapy fails to eradicate *H. pylori*, endoscopy should be carried out and culture with standard antimicrobial testing should be done due to high chances of drug-resistant organism. In India, studies have shown very high prevalence of *H. pylori* drug resistance. Metronidazole resistance varies from 70% to 80%; clarithromycin resistance varies from 17% to 45% and amoxicillin resistance varies from 20% to 50% [137–139]. However, levofloxacin and tetracycline resistance is less commonly reported with prevalence of less than 10% [137, 138]. Testing for antimicrobial resistance after failure of second-line therapy may help to optimize combination therapy for better outcome.

Statement 19: Detection of *H. pylori* genetic virulence factors and the study of host genetic polymorphism are not helpful in management of *H. pylori* infection.

Level of evidence: III

Grade of recommendation: C

Agreement: 100%.

The genetic structure of *H. pylori* is one of the most important determinants of its virulence. Variable virulence of *H. pylori* strains as well as host genetic polymorphism has been documented to contribute to the pathogenesis of various diseases caused by *H. pylori* [140]. However, due to inconclusive results and absence of therapeutic implications, genetic studies are not recommended for clinical use at present [125].

Helicobacter pylori: treatment and retreatment

Statement 20: Therapy for *H. pylori* eradication should be based on the current local antimicrobial resistance pattern if available.

Level of evidence: II-1

Grade of recommendation: A

Agreement: 100%.

There is a rising trend of antimicrobial resistance of *H. pylori* to all the commonly used antibiotics globally, including clarithromycin, metronidazole, and levofloxacin [141]. The rising resistance relates to the frequency of consumption of these antibiotics [142]. The rising antibiotic resistance is a major reason for the reduced eradication rates of *H. pylori* following treatment. As the success of a particular regimen depends on the resistance to particular antibiotics in the regimen, the treatment policy should depend on the local antibiotic resistance pattern, where available. In a multicentric study from India comprising of *H. pylori* isolates from patients across hospitals from Chandigarh, Chennai, Hyderabad, New Delhi, and Lucknow, it was noted that the prevalence of resistance of *H. pylori* was high for metronidazole, moderate for clarithromycin and amoxicillin, and low for ciprofloxacin and tetracycline with significant geographic variation [143]. Different antibiotic susceptibility pattern were reported from various areas in India in published studies [41, 139, 144–147].

Statement 21: The currently recommended first-line therapy for *H. pylori* infection in areas with low clarithromycin resistance includes a combination of PPI, amoxicillin, and clarithromycin.

Level of evidence: I
Grade of recommendation: A
Agreement: 100%.

Triple therapy with PPI, amoxicillin, and clarithromycin is a standard and age-old treatment regimen for *H. pylori* infection. Rising rates of *H. pylori* resistance to clarithromycin is a concerning issue. However, the clarithromycin-based standard triple therapy still remains an effective therapeutic option in regions with low clarithromycin resistance. Studies from Japan, Thailand, Hong Kong, and China have shown *H. pylori* eradication rates of > 90% with triple therapy combining PPI, amoxicillin, and clarithromycin given for 10 to 14 days with the eradication rate reaching up to 100% with 14 day therapy in patient population with low prevalence of clarithromycin resistance [148–151]. The high cure rate observed in these studies was independent of the CYP2C19 genotype, which affects PPI metabolism and antimicrobial susceptibility. In a study from northern India, Gehlot et al. reported clarithromycin resistance in 11.8% of *H. pylori* isolates, which was attributed to 23S rRNA gene mutations [147].

Statement 22: There is escalating rate of *H. pylori* resistance to clarithromycin and metronidazole resulting in diminished efficacy of PPI-based triple therapy.

Level of evidence: II-1
Grade of recommendation: A
Agreement: 100%.

The prevalence of metronidazole resistance is high in India [139, 143–147, 152]. In a multicenter study published in 2003, the overall prevalence of metronidazole-resistant *H. pylori* isolates was 77.9% with the prevalence varying from 37.5% to 100% among various centers in India [143]. Recently, Gehlot et al. in a multicenter study from northern India [147], Pandya et al. from Gujarat [139], and Vagarali et al. from Karnataka [146] reported high prevalence of metronidazole resistant *H. pylori* isolates, i.e. 48.5%, 83.8%, and 100% respectively. Bhatia et al. from New Delhi [144] and Datta et al. from Kolkata [145] reported a 0% prevalence of clarithromycin resistance among *H. pylori* isolates in 2004 and 2005, respectively, while more recently Gehlot et al. reported a prevalence of 11.8% from various centers in New Delhi, Kolkata, and Uttar Pradesh in 2016 [147]. The prevalence of clarithromycin resistance was reported as 58.8% in central Gujarat in 2014 [139]. The increasing trend of resistance to clarithromycin and metronidazole among *H. pylori* isolates was also reported globally [141]. It was shown that as the resistance to clarithromycin increases over a period of time [153], the efficacy of clarithromycin-based triple therapy also decreases [154].

Statement 23: Imidazole-based triple therapy regimes should not be used for eradicating *H. pylori*.

Level of evidence: I
Grade of recommendation: A
Agreement: 85.8%.

In a randomized controlled trial from northern India, Bhatia et al. have shown that triple combination therapy of lansoprazole, amoxicillin, and tinidazole was inferior to a combination of lansoprazole, amoxicillin, and clarithromycin. The *H. pylori* eradication rate was only 42.3% with the imidazole-based triple therapy on per-protocol analysis, while metronidazole resistance was found in 41.9% of *H. pylori* isolates in this study. The poor outcome of *H. pylori* eradication among the patients who received the tinidazole-based triple therapy was found to be independent of the susceptibility results [144]. High prevalence rates of imidazole resistance among *H. pylori* isolates were reported from various areas of India. Hence, triple therapy regimens containing imidazole should not be used for treating *H. pylori* infection [139, 143, 145–147, 152].

Statement 24: The duration of therapy should be 14 days for triple therapy, concomitant therapy, hybrid therapy, and quadruple therapy in India. Underdosing and lesser duration of therapy should be avoided.

Level of evidence: I
Grade of recommendation: A
Agreement: 100%.

For *H. pylori* eradication, a longer duration of therapy is better irrespective of the type of regimen used. Bhasin et al. compared combination triple therapy of lansoprazole, amoxicillin, and clarithromycin given for either 1 week or 2 weeks in a randomized controlled trial; they found that *H. pylori* eradication rate was higher with the 2-week therapy [155]. Chaudhary et al. evaluated the combination triple therapy of lansoprazole, amoxicillin, and tinidazole given for 1 week, 2 weeks, or 3 weeks in a randomized controlled trial and the *H. pylori* eradication rates were 47.6%, 80%, and 91.3%, respectively with different duration of treatment. These data proved that the longer the duration of therapy is associated with higher eradication rate of *H. pylori* [156]. Calvet et al. performed a meta-

analysis, which evaluated the triple therapy combination of PPI, clarithromycin, and either metronidazole or amoxicillin for *H. pylori* treatment and they found that 10–14-day therapies were better than the 7-day treatment regimens [157]. They also reported that in head to head comparisons, the 2 weeks' schedules were better than 1-week therapy regimens [157]. In a Cochrane database meta-analysis, it was found that prolonging the duration of PPI triple therapy from 1 to 2 weeks significantly improved the *H. pylori* eradication rate irrespective of the type and dosage of antimicrobial used. Furthermore, with triple therapy regimen of PPI, clarithromycin, and amoxicillin, superior rates of *H. pylori* eradication were observed with 14 days compared to 10-day therapy [158].

In a prospective multicentric study from Spain, it was found that an optimized concomitant treatment regimen of high-dose PPI, amoxicillin, clarithromycin, and metronidazole (4 drugs/quadruple therapy) administered for 2 weeks was superior to an optimized triple therapy regimen of high-dose PPI, amoxicillin, and clarithromycin administered for 2 weeks with *H. pylori* eradication rate of over 90% with the 2-week optimized concomitant treatment regimen [159].

In a randomized controlled trial, Ashokkumar et al. compared the hybrid therapy regimen of 2 weeks of omeprazole and amoxicillin with addition of clarithromycin and metronidazole during the last 1 week with 10-day sequential therapy regimen of omeprazole and amoxicillin for the first 5 days followed by omeprazole, clarithromycin, and metronidazole. They found significantly superior results with the 2-week hybrid therapy; the *H. pylori* eradication rate was 88.3% with the hybrid therapy on intention to treat analysis [160]. In a recently performed meta-analysis, the mean rates of *H. pylori* eradication with 14 days hybrid therapy were 88.5% and 93.3% on intention to treat and per-protocol analyses, respectively [161].

Fischbach et al. performed a meta-analysis of first-line anti-*H. pylori* quadruple therapies that showed superior efficacy of bismuth-based quadruple therapy with bismuth, metronidazole, tetracycline, and gastric acid inhibitor when administered for 10–14 days compared to shorter duration therapy of 7 days or less [162]. In a Cochrane meta-analysis published in 2013 with regard to bismuth quadruple therapy, there was a higher *H. pylori* eradication rate with 2 weeks of histamine-2 receptor antagonist (H_2RA) bismuth quadruple therapy compared to 1 week treatment, though such a benefit with extended treatment to 10 or 14 days was not seen with PPI bismuth quadruple therapy [158].

Statement 25: In patients with failure of PPI–clarithromycin–amoxicillin triple therapy, a bismuth-containing quadruple therapy or concomitant non-bismuth quadruple therapy is recommended as a second-line treatment.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%.

If first-line triple therapy with PPI–clarithromycin–amoxicillin fails to eradicate *H. pylori*, using a bismuth-based quadruple therapy is a good option. In a meta-analysis of 38 randomized controlled trials, the pooled *H. pylori* eradication rate with the combination of bismuth, PPI, metronidazole, and tetracycline was 78% in patients who experienced failure with standard clarithromycin-based triple therapy [163]. Quadruple therapy with esomeprazole, bismuth, amoxicillin, and levofloxacin has been found to be effective with *H. pylori* eradication rate of >90% in patients in whom triple therapy failed [164]. The combination of PPI, amoxicillin, tetracycline, and metronidazole concomitant quadruple therapy was found to have similar efficacy as bismuth-based quadruple regimen with *H. pylori* eradication rate of ~ 90% in a randomized controlled trial in patients in whom first-line clarithromycin-based triple therapy failed [165].

Statement 26: Fluoroquinolone-based concomitant therapy may be used after failure of second-line therapy.

Level of evidence: I

Grade of recommendation: A

Agreement: 93.4%

The use of combination triple therapy of levofloxacin/amoxicillin/PPI as a third-line treatment regimen after failure of clarithromycin-based triple therapy and bismuth-based quadruple therapy resulted in *H. pylori* eradication rates between 70% and 85% on intention to treat analyses [166–168]. The efficacy of quinolone-based rescue therapy following failure of non-bismuth quadruple therapy was assessed in a meta-analysis; the *H. pylori* eradication rates with the 10-day levofloxacin/amoxicillin/PPI triple therapy, 14 day moxifloxacin/amoxicillin/PPI triple therapy, and levofloxacin/bismuth-containing quadruple therapies were 80%, 80%, and over 90%, respectively in this meta-analysis [169]. The levofloxacin/bismuth-containing quadruple or concomitant therapy was the most efficient regimen as found in this meta-analysis.

Statement 27: Concomitant therapy is preferred to sequential therapy in regions with high antimicrobial resistance.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%

Multiple meta-analyses published earlier with regard to the comparative effectiveness of various treatment regimens for *H. pylori* had shown similar results with concomitant and sequential therapies for *H. pylori* eradication [170–174]. In a randomized controlled trial published from Puducherry by Das et al., the difference in the eradication rates of *H. pylori* with concomitant therapy or sequential therapy given for 10 days was not significant [175]. However, in a recent updated meta-analysis, Wang et al. reported that the 10-day concomitant therapy was superior to the 10-day sequential therapy for *H. pylori* eradication. Concomitant therapy proved to be more effictive than sequential therapy for eradicating *H. pylori* with regard to both metronidazole-resistant strains and those resistant to metronidazole and clarithromycin [176].

Statement 28: In areas with high clarithromycin resistance, bismuth-based quadruple therapy is recommended as first-line therapy for eradicating *H. pylori*.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%.

Pai et al. reported similar efficacy for bismuth-based quadruple therapy and clarithromycin-based triple therapy as the first-line treatment for *H. pylori* infection in Indian patients; the eradication rates of 85% to 88% were found with either of these therapies on per-protocol analysis [177]. With the emergence of clarithromycin resistance, the *H. pylori* eradication rate with the combination triple therapy of PPI/amoxicillin/clarithromycin was only 25% to 61%, while the *H. pylori* eradication rate with quadruple therapy of gastric acid inhibitor/bismuth/metronidazole/tetracycline was 90% to 100% as reported by Fischbach et al. in a meta-analysis [162]. The quadruple regimen of PPI/bismuth/amoxicillin/tetracycline logically not only overcomes clarithromycin resistance but is also unaffected by metronidazole resistance [178]. Bismuth-based quadruple therapy with rabeprazole, minocycline, amoxicillin, and bismuth achieved *H. pylori* eradication rates of nearly 90% when this was employed as first-line therapy in a region with clarithromycin resistance rates of ~ 39.7% [179].

Statement 29: In patients with failure of a bismuth-based quadruple therapy, either a fluoroquinolone-containing triple or quadruple therapy is recommended.

Level of evidence: 11-2

Grade of recommendation: B

Agreement: 100%

Gisbert reported a *H. pylori* eradication rate of 73% on intention to treat analysis with a 10-day treatment regimen of omeprazole/amoxicillin/levofloxacin after two consecutive eradication failures with clarithromycin-based triple therapy and bismuth-based quadruple therapy [180]. Jeong et al. reported a *H. pylori* eradication rate of 57.1% with PPI/amoxicillin/levofloxacin after failure of first-line therapy with clarithromycin-based triple therapy regimen and second-line therapy with bismuth-based quadruple regimen [181]. Yun et al. reported a *H. pylori* eradication rate of 65% with a 7-day treatment regimen of lansoprazole/rifaximin/levofloxacin after failure of first-line regimen with clarithromycin-based triple therapy and second-line regimen with bismuth-based quadruple therapy [182]. Noh et al. reported an overall *H. pylori* eradication rate of 65.5% with a 7–14 day third-line rescue therapy regimen of PPI/amoxicillin/levofloxacin after failure of first-line regimen with clarithromycin-based triple therapy and second-line regimen with bismuth-based quadruple therapy and the *H. pylori* eradication rate reached up to 93.3% with the 14-day levofloxacin-based third-line rescue therapy [183].

Statement 30: Hybrid therapy is another alternative for first- and second-line treatment failures.

Level of evidence: I

Grade of recommendation: A

Agreement: 100%

Hybrid therapy regimen for *H. pylori* infection consists of PPI + amoxicillin for first 5–7 days, to be followed by PPI + amoxicillin/clarithromycin/nitroimidazole during the last 5–7 days. Hybrid therapy was found to yield similar *H. pylori* eradication rate as that of sequential therapy or concomitant therapy in a meta-analysis comparing these therapies [184]. In a study conducted in Indian patients, hybrid therapy was found to be superior to sequential therapy in *H. pylori* eradication [160]. In a pooled analysis of patients who received hybrid therapy, *H. pylori* eradication occurred in 92.9% with isolated clarithromycin resistance, 97.6% with isolated metronidazole resistance, and 80% with dual clarithromycin and metronidazole resistance [185]. Hybrid therapy was found to have similar *H. pylori* eradication rate as that of bismuth-based quadruple therapy in an area with moderate rate of clarithromycin and metronidazole resistance, with the hybrid therapy regimen being relatively less affected by metronidazole resistance compared to bismuth-based quadruple therapy [186].

Statement 31: All treatment failures should be treated with a regimen that does not include major components of the failed first-line therapy.

Level of evidence: 11-2

Grade of recommendation: B

Agreement: 100%

In patients in whom the first-line therapy for *H. pylori* failed, second-line triple therapy with alternate antibiotics especially by changing clarithromycin or metronidazole from the failed regimen led to effective *H. pylori* eradication rates ranging from 85.7% to 92.9% on per-protocol analysis [187]. In another study including patients who failed first-line therapy with PPI/amoxicillin/clarithromycin, the 2nd-line regimen with PPI/amoxicillin/metronidazole led to a superior *H. pylori* eradication rate of 91.4% as compared to an eradication rate of just 62.1% with repetition of the clarithromycin-based triple therapy regimen [188]. In yet another study investigating the efficacy of ranitidine bismuth citrate (RBC)–based second-line therapies in those patients who failed first-line therapy with PPI/amoxicillin/clarithromycin, RBC-based regimens with clarithromycin namely RBC/amoxicillin/clarithromycin and RBC/clarithromycin/tinidazole had sub-optimal *H. pylori* eradication rates of 43% and 62% respectively as compared to an eradication rate of 81% with a non-clarithromycin-based regimen of RBC/amoxicillin/tinidazole [189].

Statement 32: In patients in whom second-line treatment fails, therapy should be directed by culture results if available. Other therapeutic options include rifabutin or furazolidone-based regimes.

Level of evidence: 1

Grade of recommendation: A

Agreement: 100%.

In a recent study from USA, antibiotic susceptibility–guided rescue therapy for *H. pylori* following failure of two other regimens showed a success rate of only 44.4% [190]; high body mass index (BMI) was more often associated with salvage therapy failure [190]. The rate of *H. pylori* eradication was 59.5% on intention to treat analysis in another recent study from Portugal which reported the efficacy of third-line culture-guided therapy [191]. In a systematic review and meta-analysis of studies which reported the efficacy of antibiotic susceptibility–based therapy used as a third-line rescue therapy for *H. pylori*, the eradication rate was 72% on intention to treat analysis [192]. Thus, the efficacy of third-line rescue therapy based on antibiotic susceptibility is moderate and there are factors beyond antibiotic susceptibility; hence, antibiotic susceptibility testing–based therapy should be considered an option as third-line rescue therapy though not mandatory.

Rifabutin is an antibiotic with antimycobacterial action and has been used in treating *H. pylori* predominantly as a rescue regimen. The effectiveness of antimycobacterial agent–based rescue therapy for *H. pylori* treatment varied from poor (32.1% eradication rate) with a 10-day regimen of PPI/rifampicin/tetracycline [193] to good (eradication rate 94.1%) with a 14-day regimen of PPI/amoxicillin/rifabutin [194]. In a meta-analysis reporting the efficacy of rescue therapy with PPI/amoxicillin/rifabutin for *H. pylori* infection, the overall *H. pylori* eradication rate with rifabutin-based regimen was only 68.4%, no better than other triple therapy regimens/bismuth-based quadruple regimen [195].

Several studies assessed the efficacy of furazolidone-based regimens for treating *H. pylori* infection. In a systematic review and meta-analysis of 18 studies, furazolidone-based regimens had superior *H. pylori* eradication rate in comparison to regimens containing other antimicrobials. The *H. pylori* eradication rate with furazolidone and bismuth-containing quadruple therapy was 92.9% on per-protocol analysis [196]. The *H. pylori* eradication rate with a furazolidone-based regimen when used as a rescue regimen was 77.6% on intention to treat analysis in another meta-analysis [197]. However, it should be noted that due to possible genotoxic and carcinogenetic effects, furazolidone is not approved for usage universally in all countries [198, 199].

Statement 33: In patients with penicillin allergy: tetracycline/doxycycline-, fluoroquinolone-, or clarithromycin-based regimens can be used.

Level of evidence: 11-1

Grade of recommendation: A

Agreement: 100%.

Amoxicillin, which is the backbone of most of the *H. pylori* treatment regimens, needs to be avoided in patients allergic to penicillin. Hence, the treatment regimens in the setting of penicillin allergy should be based on clarithromycin or tetracycline group or fluoroquinolone to avoid amoxicillin.

Quadruple therapy with PPI/bismuth/tetracycline/metronidazole was found superior to triple therapy with PPI/clarithromycin/metronidazole for treating *H. pylori* infection in patients allergic to penicillin with eradication rates of 75% and 59%, respectively on intention to treat analysis. In patients in whom *H. pylori* could not be eradicated with first-line therapy with either of these regimens, second-line rescue therapy with PPI/clarithromycin/levofloxacin combination achieved *H. pylori* eradication of 64% on intention to treat analysis [200]. Addition of bismuth to a combination of PPI/clarithromycin/metronidazole improved *H. pylori* eradication rates by 21% to 26%, resulting in a *H. pylori* eradication rate of 96% on per-protocol analysis in penicillin-allergic patients who have high rates of resistance to metronidazole and clarithromycin [201]. A combination of PPI/sitafloxacin/metronidazole was also found to be highly effictive in eradication of *H. pylori* in patients who are allergic to penicillin [202]. Success with doxycycline-containing regimens was found to be similar to that of tetracycline-containing regimens [203].

Recently, Vonoprazan, a novel potassium competitive acid blocker, in combination with either clarithromycin/metronidazole or sitafloxacin/metronidazole given for 7 days was found to have *H. pylori* eradication rates of more than 90% on intention to treat analysis in patients allergic to penicillin [204].

Statement 34: A high recurrence rate of *H. pylori* has been observed in India.

Level of evidence: 11-2

Grade of recommendation: B

Agreement: 100%.

India is a developing country and falls in the medium category based on the human development index. It has been observed that the global recurrence rate of *H. pylori* following eradication therapy inversely correlates with the human development index [205] and was more in developing countries compared to developed countries [206]. Though a low reinfection rate of *H. pylori* after eradication therapy was reported from Mumbai in 2000 [207], a subsequent study from Hyderabad, which analyzed the fluorescent amplified fragment length polymorphism (FAFLP) pattern of *H. pylori* pre- and post-treatment, reported a high rate of *H. pylori* reinfection which appeared mainly due to recrudescence of infection secondary to incomplete eradication [208].

Helicobacter pylori: GC and prevention/public health

Statement 35: *H. pylori* eradication reduces the risk of development of gastric neoplasms.

Level of evidence: I

Grade of recommendation: A

Agreement: 86.4%

H. pylori is accepted as an important risk factor for GC. There are various direct and indirect evidences in the form of epidemiological, molecular, animal, and eradication studies in humans to suggest that *H. pylori* is indeed a risk factor for GC [125]. Studies have shown higher frequency of isolation of *H. pylori* in patients with GC [209], while other studies have shown regression or lower rate of occurrence or recurrence of the tumor in patients in whom the infection was eradicated [210]. The strongest evidence that *H. pylori* eradication reduces the risk of development of GC came from randomized interventional trials from China [211, 212]. Meta-analyses also revealed a strong relationship between *H. pylori* and GC [213, 214]. A recent Cochrane meta-analysis has also shown significant protective effect of *H. pylori* eradication on future occurrence of GC [38].

An Indian enigma of very high prevalence of *H. pylori* infection and low frequency of GC has been described in review articles. A few studies showed low frequency of intestinal metaplasia in Indian patients with *H. pylori* infection [215–217]. There are few case-control studies, which failed to show an association between *H. pylori* infection and GC. In a study on 50 patients with gastric neoplasms and 50 controls with non-ulcer dyspepsia, *H. pylori* infection was detected less frequently in GC patients (38%, 19/50) than those with non-ulcer dyspepsia (68%, 34/50) [218]. Another study demonstrated that 64.7% (33/51) patients with GC and 74.4% (32/43) with non-ulcer dyspepsia had infection with *H. pylori* [39]. These studies can be criticized due to small sample size with a consequent type II statistical error. Also, in most of these studies, endoscopy-based tests were used to diagnose *H. pylori* infection. Endoscopy-based tests can be false negative in patients with GC due to gastric atrophy and intestinal metaplasia. A two centre study from Lucknow and Kolkata had taken a better sample size of 279 patients with gastric neoplasms (263 GC and 16 primary gastric lymphoma). This study also failed to show a higher frequency of *H. pylori* infection in patients with gastric neoplasms as compared with the controls (101 non-ulcer dyspepsia and 355 healthy subjects) [219].

Despite strong evidence in the form meta-analysis and randomized interventional studies showing that *H. pylori* eradication reduces the risk of gastric neoplasms, due to low frequency of GC in Indian population (which is an enigma), routine *H. pylori* eradication to prevent GC in Indian population cannot be recommended.

Statement 36: Early *H. pylori* eradication prevents progression to pre-neoplastic lesions.

Level of evidence: I

Grade of recommendation: A

Agreement: 81.8%.

Correa proposed the stepwise progression of normal gastric mucosa to GC in *H. pylori*–infected patients [220]. *H. pylori* initially causes inflammation of gastric mucosa resulting in chronic active gastritis which progresses into pan gastric atrophy. Then intestinal metaplasia develops which may convert into dysplasia and ultimately into cancer. Several studies and meta-analysis have shown significant association of *H. pylori* infection and precancerous lesions such as atrophic gastritis and intestinal metaplasia [221].

A significant observation is that although *H. pylori* eradication heals chronic active gastritis and reverses gastric atrophy, it does not affect intestinal metaplasia. This may be associated with a certain restitution of glands with specialized cells, and thus a reduction of atrophic gastritis. Systematic reviews and meta-analysis have also shown that *H. pylori* eradication favors arrests of precancerous lesions such as atrophic gastritis (but not intestinal metaplasia) into progressing into GC [222, 223]. Intestinal metaplasia cannot be reversed although its progression is halted in a large

subset of patients [224]. There is scarcity of data in the Indian context.

Statement 37: The limited data available from India suggest that in spite of high *H. pylori* seropositivity, its relationship with GC development is debatable.

Level of evidence: II 2

Grade of recommendation: C

Agreement: 90.9%

A few case-control studies [39, 218, 219] from India do not show any relationship of GC and *H. pylori* seropositivity. The Indian enigma of high *H. pylori* seropositivity and low prevalence of GC has also been discussed [215]. The case-control studies from India can be criticized as these suffer from small sample size. It is also thought that by the time GC develops, the background gastric mucosa may be atrophic and may not permit *H. pylori* colonization. Hence, the case-control studies may not reflect whether the bacteria were present before the onset of GC. Thus, data from India have limitation and large multicentric studies are required to establish the role of *H. pylori* in GC in India.

Statement 38: There is insufficient data in favor of widespread *H. pylori* eradication to prevent GC in India.

Level of evidence: III

Grade of recommendation: C

Agreement: 95.5%

Maastricht V/Florence Consensus Report recommendations suggest that *H. pylori* eradication for GC prevention is cost-effective in communities with a high risk for GC [125]. These recommendations are based on the economy-based modeling studies that have evaluated the cost-effectiveness *H. pylori* screen-and-treat policies for the prevention of GC. The benefit is likely to be highest in communities with a high risk of GC where all these randomized trials were conducted. However, in developed countries and countries like India where the prevalence of GC is low, long-term studies are required to gauge the cost-effectiveness of such a strategy of mass *H. pylori* eradication.

Statement 39: A screen-and-treat strategy for *H. pylori* may be considered even in India among individuals at increased risk for GC.

Level of evidence: III

Grade of recommendation: C

Agreement: 81.8%

Maastricht IV guidelines indicated that screen-and-treat should be explored in communities with a significant burden of GC because several randomized clinical trials had shown a 30% to 40% reduction in GC risk in those in whom *H. pylori* had been successfully eradicated [125].

The individuals who are at increased risk of GC are those persons who have corpus predominant gastritis, gastric atrophy/intestinal metaplasia, hypochlorhydria, and family history of GC. Population screening by invasive approaches is not feasible especially in regions of low gastric malignancy. The Asia Pacific consensus also suggests that even in countries with relatively low prevalence of GC, modeling suggests that a "screen and treat" strategy may be cost-effective at a level that may even exceed that of breast cancer and cervical cancer screening [3]. Thus, the strategy of screen and treat should be considered even in India among individuals at increased risk for GC.

Conclusions

There is an increasing prevalence of resistance to metronidazole and clarithromycin in India, which is responsible for reduced efficacy of the PPI-based triple therapies, which are available in India. Since the choice of the regime to be used would depend on the local resistance pattern, it is important that periodic resistance pattern is evaluated in different regions of India, which is a large country with varying *H. pylori* resistance pattern. In this regard, the national regional research laboratories including the Indian Council of Medical Research should conduct periodic *H. pylori* sensitivity surveys, and the results be made available to the physicians and professional bodies like ISG to enable rational optimal antimicrobial regime for *H. pylori* therapy, which could vary from region to region.

Salvage therapies include standard triple therapy that have not been previously used, bismuth-based quadruple therapy, levofloxacin-based therapy, or rifabutin-based triple therapy. Smoking cessation and changing the dose or choice of PPI may improve eradication rates. The role of antibiotic sensitivity testing was not addressed specifically, but it should be considered for surveillance of trends in antibiotic resistance, as well as in selected cases to guide salvage therapies. In most cases, however, it will not influence the choice of second- or third-line therapies.

Furthermore, there is an urgent need for the involvement of the pharmaceutical industry to be proactive and spearhead research in the field of *H. pylori* treatment, and also to make bismuth-based quadruple therapy widely available in India to tackle the problem of multi-resistant *H. pylori* strains.

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Compliance with ethical standards

Conflict of interest VA, UCG, GM, UD, SAZ, JV, AKD, AKM, AS, BRT, KV, MS, MKS, NR, PA, PCD, PR, SKS, SB, SP, UG, UP, VPM, and VK declare that they have no conflict of interest in relation to this paper.
SPS owns stock for Sun Pharmaceutical Industries Ltd., Torrent Pharmaceuticals Ltd., Dr. Reddy's Laboratories, and Panacea Biotec.

Ethical statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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