REVIEW ARTICLE

Clinical Management of Helicobacter pylori Infection in China
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Keywords
Helicobacter pylori, treatment, bismuth quadruple therapy, furazolidone.

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Abstract
Helicobacter pylori (H. pylori) infection has been associated with gastric disorders. The situation of H. pylori infection in China—where a high prevalence of H. pylori infection, a high incidence of gastric cancer, and widespread resistance to clarithromycin, metronidazole, and levofloxacin exist—is quite different from that in Western countries. In order for Chinese clinicians to better manage H. pylori infection, a Chinese Study Group on H. pylori published four consensus reports regarding the management of H. pylori infection in China between 1999 and 2012. The eradication rate with standard triple therapy was <80% in most areas of China. Bismuth is available in China, and bismuth-containing quadruple therapy has been shown to produce a high eradication rate; thus, bismuth quadruple therapy could be recommended both as an initial and as a rescue therapy in China. There is no advantage of sequential therapy over triple therapy in Chinese patients, but the efficacy of concomitant therapy must be studied further. This review introduces the epidemiology, diagnosis, indicators, and therapies for the eradication of H. pylori in China in recent years.

Helicobacter pylori (H. pylori) is a gram-negative, spiral-shaped pathogenic bacterium that was first identified by Marshall and Warren in 1983 [1]. During the past 30 years, considerable research has focused on this bacterium and has revealed that H. pylori infection may result in chronic gastritis, ulcers, and stomach cancer in 1% of the infected population [2, 3]. Although eradication of the infection has been achieved by the use of clarithromycin- or metronidazole-based triple therapies, antibiotic resistance has diminished the cure rate to less than 80%[4]. More than 50% of the Chinese population is infected with H. pylori, and the antibiotic resistance demonstrated by this bacterium is quite serious. The clinical management of H. pylori infection in China is reviewed here.

Epidemiology
Articles related to the epidemiology of H. pylori infection in adults in China that were retrieved in a search of the PubMed database. The prevalence of H. pylori infection ranges from 41.35% to 72.3% and may vary with the population studied and with the geographic area (Table 1).

It is worth noting that there has been an obvious decline in the prevalence of H. pylori infection in China, particularly in some of the more developed provinces. In the city of Guangzhou, Chen et al. studied the rates of H. pylori infection in 1993 and 2003 via ELISA. The H. pylori infection rate was reported as 63.2% in 1993, and it declined to 49.3% in 2003, which suggests that the seroprevalence of H. pylori infection significantly decreased in Guangzhou during that 10-year period. This change may be attributable to the improvement in the socioeconomic conditions in this city [7]. This result has also been verified by other studies. The H. pylori infection rate among rural laborers in Dongguan is 57.9%, while in Beijing and Dalian, the infection rate seems to be substantially lower [8, 14].

Helicobacter pylori was listed as a class I carcinogenic factor by the IARC in 1994 [16], and interestingly, the incidence of gastric cancer is also very high in China. The city of Wuwei, located in northwest China, has a particularly high incidence of gastric cancer (91.18/100,000 from 2001 to 2002) [17]. According to research conducted in children and teenagers, the infection rate of H. pylori in 2006–2007 was as high as 72.3% (678/938) in Wuwei. Similar results were also been
identified in Linyu and Changle in the last century. The prevalence of *H. pylori* infection was correlated with the type of dwelling, the occupation of the parents, the source of drinking water, the consumption of raw vegetables, kindergarten attendance, poor oral hygiene, and breast feeding, among other factors [12]. The rate of *H. pylori* infection was also high (63.14%, 3435/5417) in Yangzhong, which is another city with a high incidence of gastric cancer [13]. Zhang et al. reported the prevalence of *H. pylori* infection in areas with high (Muping County, Shandong) and low (Yanqing County, Beijing) incidences of gastric cancer. The prevalence of *H. pylori* infection in adults was 50.95% in Muping, which was significantly higher than the 41.35% infection rate in Yanqing [11]. Similar results were also obtained in studies of children from these cities [11].

### Indications for *H. Pylori* eradication

Table 2 lists the indications for the treatment of *H. pylori*-positive patients according to the recommendations of the Chinese Society of Gastroenterology and to those of the Chinese Study Group on *H. pylori* published in 2013 [18].

Compared with the previous consensus report published in 2008 [19], the following three items were added to this new version: (1) early gastric cancer resected endoscopically or by subtotal gastrectomy, (2) a plan for long-term use of NSAIDs (including low-dose aspirin), and (3) the long-term use of proton-pump inhibitors.

To combat the high incidence of gastric cancer in China, the “test and treat” strategy recommended by several consensus reports may cause missed diagnoses of gastric cancer and therefore is not recommended in China [18]. The concomitant treatment of patients for gastroesophageal reflux disease (GERD) and for the eradication of *H. pylori* has also been discussed in the new consensus report. Although the eradication of

### Table 1 *Helicobacter pylori* epidemiology in asymptomatic individuals in China

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Years of specimen collection</th>
<th>n</th>
<th><em>H. pylori</em> prevalence, %</th>
<th>Diagnostic method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hong Kong</td>
<td>1993–1994</td>
<td>397</td>
<td>58.4</td>
<td>ELISA</td>
</tr>
<tr>
<td>Jiang et al. [6]</td>
<td>Linqu</td>
<td>1994</td>
<td>218</td>
<td>71.1</td>
<td>13C-UBT</td>
</tr>
<tr>
<td>Chen et al. [7]</td>
<td>Guangzhou</td>
<td>1993</td>
<td>830</td>
<td>63.2</td>
<td>ELISA</td>
</tr>
<tr>
<td></td>
<td>Guangzhou</td>
<td>2003</td>
<td>1471</td>
<td>49.3</td>
<td>ELISA</td>
</tr>
<tr>
<td>Chen et al. [8]</td>
<td>Beijing</td>
<td>2003</td>
<td>1232</td>
<td>46.7</td>
<td>13C-UBT</td>
</tr>
<tr>
<td>Chen et al. [9]</td>
<td>Shanghai</td>
<td>2004–2004</td>
<td>1925</td>
<td>66.4</td>
<td>14C-UBT and ELISA</td>
</tr>
<tr>
<td>Zeng et al. [10]</td>
<td>Dongguan</td>
<td>2007</td>
<td>658</td>
<td>57.9</td>
<td>14C-UBT or ELISA</td>
</tr>
<tr>
<td></td>
<td>Yanqing</td>
<td>2006</td>
<td>503</td>
<td>41.35</td>
<td>HpSA</td>
</tr>
<tr>
<td>Zhang et al. [12]</td>
<td>Wuwei</td>
<td>2006–2007</td>
<td>938</td>
<td>72.3</td>
<td>HpSA</td>
</tr>
<tr>
<td>Hu et al. [14]</td>
<td>Dalian</td>
<td>2010</td>
<td>3995</td>
<td>44.9</td>
<td>ELISA</td>
</tr>
<tr>
<td>Chen et al. [15]</td>
<td>Changsha</td>
<td>2011–2013</td>
<td>2264</td>
<td>47.2</td>
<td>13C-UBT</td>
</tr>
</tbody>
</table>

### Table 2 Recommended indications for *Helicobacter pylori* infection and the degrees of recommendation [18]

<table>
<thead>
<tr>
<th><em>H. pylori</em>-positive diseases</th>
<th>Strongly recommended</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer (regardless of complications or whether ulcer is active or inactive)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Gastric MALT lymphoma</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chronic gastritis with dyspepsia</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chronic gastritis with gastric mucosal atrophy/erosion</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Early gastric cancer resected endoscopically or by subtotal gastrectomy</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Long-term use of proton-pump inhibitor</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Family history of gastric cancer</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Planning to take long-term NSAIDs (including low-dose aspirin)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>IDA of unknown cause</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>ITP</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Other <em>H. pylori</em>-related diseases (e.g., lymphocytic gastritis, gastric hyperplastic polyps, Ménétrier disease)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Requested by individual patient</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

IDA, iron deficiency anemia; ITP, idiopathic thrombocytopoietic purpura; MALT, mucosa-associated lymphoid tissue; NSAIDs, non-steroidal anti-inflammatory drugs.
H. pylori might increase the risk of developing GERD in individuals who live in East Asia [20, 21], long-term users of PPIs who are infected with H. pylori may have increased risks for gastric atrophy and gastric cancer [22]. Therefore, patients with GERD who receive long-term treatment with PPIs should also receive treatment for the eradication of H. pylori [18].

**Helicobacter Pylori and gastric cancer screening**

**Helicobacter pylori** is the class I carcinogen, meanwhile, China listed in the high prevalence of gastric cancer and H. pylori infection. According to the early stage gastric cancer screening and endoscopic diagnosis and consensus in China [23], subject over 40 years of age and satisfied one of the following conditions (1. In the high prevalence area of gastric cancer; 2. H. pylori infection; 3. Gastric precancerous diseases such as chronic atrophic gastritis, gastric ulcer, gastric polypus, gastric remnant, hypertrophic gastritis, or pernicious anemia; 4. First-degree relatives to gastric cancer patients; 5. Other gastric cancer risk factors such as high salt or pickles diet, smoking, excessive drinking) should be listed as screening object. The screening method including pepsinogen and H. pylori antibody detection. The critical value of PG serum detection is PG I ≤70 μg/L and PG I/PG II ≤7.0. According to the gastric cancer risk, the screening result could be classified into four levels. Level A, PG (−) and H. pylori (−), no further endoscope is needed; Level B, PG (−) and H. pylori (+), once endoscope examination should be checked within every 3 years; Level C, PG (+) and H. pylori (+), once endoscope examination should be checked within every 2 years; Level D, PG (+) and H. pylori (−), endoscope examination should be checked every year; the level of PG is stable in the short term, the screening test could be repeated about 5 years.

**Detection of H. Pylori infection**

The current methods for the clinical detection of H. pylori infection can be divided into two groups: invasive detection and noninvasive detection. Current H. pylori infection may be diagnosed when one of the following three methods of detection is positive: (1) Rapid urease test (RUT); (2) 13C- or 14C-UBT; and (3) HpSA detection. The efficacy of H. pylori treatment should be evaluated 4 weeks after eradication therapy. If any of the above-mentioned three tests is negative, H. pylori eradication may be diagnosed [18].

The reagents and methods that are used to assess H. pylori infection in clinical practice must be verified. Some medicines such as antibiotics, bismuth, or traditional Chinese medicine may interfere with the results of these tests [24]; furthermore, diseases such as gastric bleeding may influence the test results [25].

**Eradication of H. Pylori infection**

**Epidemiology of antibiotic resistance in China**

The eradication rate after standard triple therapy (PPI + clarithromycin + metronidazole/amoxicillin) has fallen below 80% in most areas of the world, which is unacceptable [4]. The reasons for this decrease may include genetic polymorphisms in CYP2C19, patient compliance, and bacterial factors; however, antibiotic resistance may be among the most important reason particularly in China.

Su et al. studied the antibiotic resistance of H. pylori that was isolated in the southeast coastal region of China and reported the resistance rates to clarithromycin, metronidazole, levofloxacin, amoxicillin, gentamicin, and furazolidone as 21.5, 95.4, 20.6, 0.1, 0.1, and 0.1%, respectively. The rates of double, triple, and quadruple antibacterial resistance were 25.5, 7.5, and 0.1%, respectively [26]. After using the E-test method to examine 374 H. pylori strains from Beijing for susceptibility to antibiotics between 2000 and 2009, Chen et al. reported that resistance to clarithromycin, metronidazole, and fluoroquinolone increased annually (from 14.8 to 65.4%, 38.9 to 78.8%, and 27.1 to 63.5%, respectively, in 2000 or 2006–2007 to 2009, respectively) [27]. Another study conducted by Sun et al. also revealed increased rates of H. pylori resistance to clarithromycin (8.6% and 20.7%) and levofloxacin (10.3% and 32.5%) from 2000 to 2009 in Shanghai [28]. Meanwhile, only one strain of H. pylori isolated in 2005 was resistant to tetracycline. In contrast, all strains were sensitive to amoxicillin and furazolidone [28]. We also monitored the antibiotic resistance of H. pylori in Jiangxi province from 2005 to 2010. A total of 121 tissue samples cultured in microaerobic conditions were identified as typical H. pylori strains by biochemical and histologic methods. The average rates of resistance to metronidazole, clarithromycin, levofloxacin, amoxicillin, and furazolidone were 72.70%, 14.88%, 14.05%, 0.83%, and 0%, respectively [29]. The resistance to clarithromycin and levofloxacin in developed area was relatively higher than remote area. However, the resistance to metronidazole shows no regional differences.

The high primary resistance to clarithromycin and metronidazole was even found in children [30–33]. Liu et al. studied the primary resistance rate to antibiotics
in children in the Beijing area. The rates of resistance to clarithromycin, azithromycin, metronidazole, levofloxacin, moxifloxacin, and rifampicin were 84.9%, 87.7%, 61.6%, 13.7%, 15.1%, and 6.8%, respectively. No resistance to amoxicillin, gentamicin, or tetracycline was observed [30].

Overall, _H. pylori_ strains in China demonstrated a high resistance to metronidazole, clarithromycin, and levofloxacin, whereas the resistance to amoxicillin, tetracycline, and furazolidone was quite low. This is very important evidence that will allow us to devise appropriate therapies for _H. pylori_ eradication in China following the principle that clinicians should use only what has been demonstrated to be effective in the local population [4].

**Standard triple therapy**

In 1998, Chu et al. published a prospective randomized trial of triple therapy (omeprazole 20 mg once daily, clarithromycin 500 mg twice daily, and metronidazole 400 mg twice daily for 1 week) to eradicate _H. pylori_. According to intention to treat (ITT) and per protocol (PP) analyses, the eradication rate reached 92% (95% CI 89.3–94.2%) and 95.2% (95% CI 92.9–97.0%), respectively [34].

However, with the rapid increase of antibiotic resistance, the most commonly recommended regimen led to an unacceptably low success rate for the treatment [4, 35–37] (Table 3.). Zheng et al. performed a study to evaluate the efficacy of triple therapy and found that the ITT eradication rate and the PP eradication rate were 63.5% and 65.1%, respectively [36]. The results were also unsatisfactory in a study in Taiwan conducted by Chen et al., who reported that neither AEC (amoxicillin, esomeprazole, and clarithromycin for 7 days) nor LEC (levofloxacin, esomeprazole, and clarithromycin for 7 days) produced an ITT eradication rate of 80%, as recommended by Graham [4, 37].

The Maastricht IV/Florence consensus report [38] recommended a first-line therapy based on clarithromycin resistance. As individuals in most areas of China demonstrate high resistance to clarithromycin, standard triple therapy should not be used in most areas in China; instead, it should only be used when the clarithromycin resistance has been verified to be < 20% [18].

The high resistance to clarithromycin and metronidazole contributes to the low _H. pylori_ eradication rate after standard triple therapy [4]. Furazolidone is an older drug that has been used to treat peptic ulcers in China, although for a long time, its mechanism of action was not well-defined. When we used furazolidone instead of clarithromycin and extended the treatment time to 10 days, the eradication rate improved to 81.32% according to ITT analysis [39].

**Bismuth-containing quadruple therapy**

In regions where individuals demonstrate high clarithromycin resistance, bismuth-containing quadruple therapy should be recommended as a first-line therapy if bismuth is available in that particular area [38]. The bismuth-containing quadruple therapy recommended by the Chinese _H. pylori_ consensus report consists of PPI, bismuth and two antibiotics. The types of antibiotics recommended by the consensus report are as follows: (1) amoxicillin + clarithromycin; (2) amoxicillin + levofloxacin; (3) amoxicillin + furazolidone; and (4) tetracycline + metronidazole or furazolidone [18]. Many prospective studies were recently performed in China, and all of these regimens seem to be highly effective in the eradication of _H. pylori_ (Table 4).

As previously mentioned, the use of standard triple therapy is not satisfactory for achieving a low eradication rate, although the efficacy of this therapy has been improved with the addition of bismuth [41, 42]. Xu et al. reported that 7 days of standard triple therapy

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**Table 3** Recently published reports on Triple therapies as a primary treatment for the eradication of *Helicobacter pylori* in China

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Region</th>
<th>Year</th>
<th>Regimen</th>
<th>Days</th>
<th>Cases</th>
<th>ITT (%)</th>
<th>PP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. [36]</td>
<td>Shanghai</td>
<td>2010</td>
<td>P (40 mg b.i.d.) + A (1 g b.i.d.) + C (500 mg b.i.d.)</td>
<td>7</td>
<td>85</td>
<td>63.5</td>
<td>65.1</td>
</tr>
<tr>
<td>Chen et al. [37]</td>
<td>Taiwan</td>
<td>2010</td>
<td>E (40 mg q.d.) + C (500 mg q.d.) + Lev (500 mg q.d.)</td>
<td>7</td>
<td>90</td>
<td>78.9</td>
<td>85.3</td>
</tr>
<tr>
<td>Chen et al. [37]</td>
<td>Taiwan</td>
<td>2010</td>
<td>E (40 mg b.i.d.) + C (500 mg b.i.d.) + A (1 g b.i.d.)</td>
<td>7</td>
<td>99</td>
<td>74.8</td>
<td>86.0</td>
</tr>
<tr>
<td>Qian et al. [40]</td>
<td>Nanjing</td>
<td>2012</td>
<td>E (20 mg b.i.d.) + Lev (500 mg b.i.d.) + A (1 g b.i.d.)</td>
<td>7</td>
<td>114</td>
<td>78.1</td>
<td>80.9</td>
</tr>
<tr>
<td>Lu et al. [39]</td>
<td>Jiangxi</td>
<td>2014</td>
<td>R (10 mg b.i.d.) + F (100 mg b.i.d.) + A (1 g b.i.d.)</td>
<td>10</td>
<td>91</td>
<td>81.32</td>
<td>88.1</td>
</tr>
<tr>
<td>Zhou et al. [35]</td>
<td>Multicenter</td>
<td>2014</td>
<td>E (20 mg b.i.d.) + C (500 mg b.i.d.) + A (1 g b.i.d.)</td>
<td>10</td>
<td>140</td>
<td>66.4</td>
<td>72.7</td>
</tr>
</tbody>
</table>

q.d., once daily; b.i.d., twice daily; E, esomeprazole; C, clarithromycin; R, rabeprazole; A, amoxicillin; Lev, levofloxacin; F, furazolidone; ITT, intention to treat; PP, per protocol.
plus bismuth increased the eradication rate from 66.67% to 82.09% according to ITT analysis [42]. When the treatment was extended to 14 days, the ITT eradication rate reached 93.7% compared with 80.0% after 7 days of treatment, which suggested that the addition of bismuth can overcome H. pylori resistance to clarithromycin [41].

As few instances of furazolidone resistance have been reported, furazolidone-based quadruple therapy is a possible regimen in China [43–45]. A multicenter randomized controlled trial was performed to evaluate the efficacy of furazolidone quadruple therapy. A total of 580 patients who were diagnosed with a duodenal ulcer and H. pylori infection and were referred to ten hospitals in Jiangxi province were enrolled in the study. Furazolidone quadruple therapy consisted of 10 mg rabeprazole, 220 mg bismuth, 1000 mg amoxicillin, and 100 mg furazolidone given twice daily for 7 or 10 days. According to the ITT analysis, the H. pylori eradication rates after 7 and 10 days were 82.8% (120/145) and 86.9% (126/145), respectively [43]. Moreover, another study performed in Shanghai reported that the H. pylori eradication rate after furazolidone–bismuth quadruple therapy reached 95%. This type of therapy should be recommended for individuals who are allergic to penicillin [44]. Some clinicians have expressed concern regarding the safety of furazolidone [46]. Jin et al. [47] reported that furazolidone induced oxidative DNA damage in an in vitro study. Dose-related increases in the incidence of both breast and bronchial adenocarcinomas have been observed in animal models, which suggests that furazolidone may be carcinogenic [48]. However, some specialists consider this to be a misunderstanding [49]. The IARC report states the following: “Furazolidone has been produced commercially since 1955. It is used in human and veterinary medicine as an antibacterial and anti-parasitic agent. No data were available to assess the teratogenicity or chromosomal effects of this compound in humans. No case report or epidemiological study of the carcinogenicity of furazolidone was available to the Working Group. Evaluation: No evaluation of the carcinogenicity of furazolidone to experimental animals could be made. In the absence of epidemiological data, no evaluation of the carcinogenicity of furazolidone to humans could be made.”[50]

Tetracycline–bismuth quadruple therapy could also achieve the desired H. pylori eradication rate in China [36, 44]. Zheng et al. [36] reported that the eradication rate for tetracycline quadruple therapy was 89.4% according to ITT analysis and 91.6% according to PP analysis. Another study performed by Liang et al. [44] also reported that tetracycline quadruple therapy could produce an rescue eradication rate in Shanghai as high as 87.9% according to ITT analysis.

In summary, bismuth-containing quadruple therapy is a highly effective regimen in China that could be recommended as a first-line therapy. However, bismuth is not available in most developed countries due to its potential nephrotoxicity [51–53]. However, the results of a meta-analysis that included 35 randomized controlled trials involving 4763 patients detected no statistically significant difference in the total number of adverse events after the use of bismuth. Bismuth is safe and effective in patients with H. pylori infection in China.

Table 4 Recently published reports on bismuth-containing quadruple therapies as a primary treatment for the eradication of Helicobacter pylori in China

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Year</th>
<th>Regimen</th>
<th>Days</th>
<th>Cases</th>
<th>ITT (%)</th>
<th>PP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. [36]</td>
<td>Shanghai</td>
<td>2010</td>
<td>BSC (220 mg b.i.d.) + T (750 mg b.i.d.) + M (400 mg t.i.d.) + L (30 mg b.i.d.)</td>
<td>10</td>
<td>85</td>
<td>89.4</td>
<td>91.6</td>
</tr>
<tr>
<td>Sun et al. [41]</td>
<td>Shanghai</td>
<td>2010</td>
<td>BPC (220 mg b.i.d.) + C (500 mg b.i.d.) + A (1 g b.i.d.) + O (20 mg b.i.d.)</td>
<td>7</td>
<td>80</td>
<td>80.0</td>
<td>82.0</td>
</tr>
<tr>
<td>Sun et al. [41]</td>
<td>Shanghai</td>
<td>2010</td>
<td>BPC (220 mg b.i.d.) + C (500 mg b.i.d.) + A (1 g b.i.d.) + O (20 mg b.i.d.)</td>
<td>14</td>
<td>80</td>
<td>93.7</td>
<td>97.4</td>
</tr>
<tr>
<td>Xu et al. [42]</td>
<td>Hunan</td>
<td>2011</td>
<td>BPC (220 mg b.i.d.) + C (500 mg b.i.d.) + A (1 g b.i.d.) + E (20 mg b.i.d.)</td>
<td>7</td>
<td>69</td>
<td>82.1</td>
<td>88.7</td>
</tr>
<tr>
<td>Lu et al. [43]</td>
<td>Jiangxi</td>
<td>2011</td>
<td>BSC (220 mg b.i.d.) + F (100 mg b.i.d.) + A (1 g b.i.d.) + R (20 mg b.i.d.)</td>
<td>7</td>
<td>145</td>
<td>82.8</td>
<td>88.9</td>
</tr>
<tr>
<td>Lu et al. [43]</td>
<td>Jiangxi</td>
<td>2011</td>
<td>BSC (220 mg b.i.d.) + F (100 mg b.i.d.) + A (1 g b.i.d.) + R (20 mg b.i.d.)</td>
<td>10</td>
<td>145</td>
<td>86.9</td>
<td>91.3</td>
</tr>
<tr>
<td>Liang et al. [44]</td>
<td>Shanghai</td>
<td>2013</td>
<td>BPC (220 mg b.i.d.) + T (500 mg q.i.d.) + F (100 mg t.i.d.)</td>
<td>14</td>
<td>108</td>
<td>91.7</td>
<td>96.1</td>
</tr>
<tr>
<td>Liang et al. [44]</td>
<td>Shanghai</td>
<td>2013</td>
<td>BPC (220 mg b.i.d.) + T (500 mg q.i.d.) + M (400 mg q.i.d.) + L (30 mg b.i.d.)</td>
<td>14</td>
<td>107</td>
<td>87.9</td>
<td>93.1</td>
</tr>
<tr>
<td>Liang et al. [44]</td>
<td>Shanghai</td>
<td>2013</td>
<td>BPC (220 mg b.i.d.) + T (500 mg q.i.d.) + A (1 g t.i.d.) + L (30 mg b.i.d.)</td>
<td>14</td>
<td>105</td>
<td>83.8</td>
<td>94.6</td>
</tr>
<tr>
<td>Liang et al. [44]</td>
<td>Shanghai</td>
<td>2013</td>
<td>BPC (220 mg b.i.d.) + A (1 g t.i.d.) + F (100 mg t.i.d.) + L (30 mg b.i.d.)</td>
<td>14</td>
<td>104</td>
<td>95.2</td>
<td>99.0</td>
</tr>
</tbody>
</table>

b.i.d., twice daily; t.i.d., three times daily; q.i.d., four times daily; BPC, bismuth potassium citrate; BSC, bismuth subcitrate; CBS, colloidal bismuth subcitrate; E, esomeprazole; L, lansoprazole; O, omeprazole; R, rabeprazole; C, clarithromycin; A, amoxicillin; F, furazolidone; T, tetracycline; M, metronidazole; ITT, intention to treat; PP, per protocol.
and well-tolerated for the treatment of *H. pylori*. The only adverse event that occurred with significant frequency was dark stools [54]. Clinicians should, however, avoid the prescription of bismuth as a gastric mucosa protectant for long-term use.

**Sequential therapy**

Sequential therapy is quite popular in Western countries, and it leads to a high eradication rate [55–57]. However, the efficacy of sequential therapy is controversial in China (Table 5).

An open-label, randomized, crossover trial was conducted in Hong Kong to evaluate the rate of *H. pylori* eradication after 10 days of sequential therapy, the eradication rate according to ITT analysis was 89.4%, and the eradication rate according to PP analysis was 95.2% [58]. The Taiwan Helicobacter Consortium also studied the influence of the treatment course on the eradication rate of *H. pylori*, which was 90.7% according to ITT analysis after 14 days of sequential therapy and 87.0% after 10 days of sequential therapy [59].

However, Zhou et al. performed a randomized multicenter trial and reported that the eradication rate of *H. pylori* after 10 days of sequential therapy was only 72.1% according to ITT analysis and only 76.5% according to PP analysis [35]. While using levofloxacin instead of clarithromycin could only little improve the eradication rate, another clinical trials in Nanjing reported that the 10-day standard sequential therapy and 10-day levofloxacin sequential therapy eradication rate were 78.3% and 82.8%, by ITT analysis, respectively [40].

The contradictory results may be explained by the different rates of resistance to antibiotics in different areas. For example, in Hong Kong, the rate of resistance to clarithromycin was only 13% in 2005 [60], whereas in Taiwan, the resistance rates of naive *H. pylori* to clarithromycin and metronidazole were 10.6% and 26.7%, respectively [61]. In mainland China, the resistance of *H. pylori* to these antibiotics was very high, as previously mentioned; therefore, sequential therapy may not provide a satisfactory eradication rate when both clarithromycin and metronidazole resistance are present, thus should not be recommended as empiric therapy in China [35].

**Concomitant therapy**

Concomitant therapy is widely studied around the world, and its eradication rate is as high as that of sequential therapy [57, 62–65]. However, no randomized, prospective clinical trials of concomitant therapy have been performed in mainland China.

In Taiwan, Kao SS et al. reported that 7 days of a concomitant regimen ( pantoprazole 40 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg twice daily for 7 days) achieved a high *H. pylori* eradication rate (93.7% by ITT and 96.4% by PP)[66]. Wu et al. [67] obtained similar results in another study, the ITT eradication rate reached 93.0% after concomitant therapy, and the authors concluded that concomitant therapy may be more suitable for patients with dual resistance to antibiotics. Future studies are needed to determine the efficacy of concomitant therapy.

**Levofloxacin-containing therapy**

Levofloxacin-containing therapy was designed to overcome the shortage of clarithromycin for standard triple therapy and was recommended as a second-line therapy. 

| Table 5 Recently published reports on sequential therapies as a primary treatment for the eradication of Helicobacter pylori in China |
|---|---|---|---|---|
| Author | Region | Year | Regimen | Cases | ITT (%) | PP (%) |
| Qian et al. [40] | Nanjing | 2012 | E (20 mg b.i.d.) + A (1 g b.i.d.) ×5 day E (20 mg b.i.d.) + C (500 mg b.i.d.) + Tin (500 mg b.i.d.) ×5 day | 115 | 78.3 | 82.6 |
| Qian et al. [40] | Nanjing | 2012 | E (20 mg b.i.d.) + A (1 g b.i.d.) ×5 day E (20 mg b.i.d.) + Lev (500 mg q.d.) + Tin (500 mg b.i.d.) ×5 day | 116 | 82.8 | 86.5 |
| Liu et al. [58] | Hong Kong | 2013 | E (20 mg b.i.d.) + A (1 g b.i.d.) ×5 day E (20 mg b.i.d.) + C (500 mg b.i.d.) + M (500 mg q.d.) ×5 day | 179 | 89.4 | 95.2 |
| Liou et al. [59] | Taiwan | 2013 | L (30 mg q.d.) + A (1 g b.i.d.) ×7 day L (30 mg q.d.) + C (500 mg b.i.d.) + M (500 mg q.d.) ×7 day | 300 | 90.7 | 94.4 |
| Liou et al. [59] | Taiwan | 2013 | L (30 mg q.d.) + A (1 g b.i.d.) ×5 day L (30 mg q.d.) + C (500 mg b.i.d.) + M (500 mg q.d.) ×5 day | 300 | 87.0 | 90.5 |
| Zhou et al. [35] | Multicenter | 2014 | E (20 mg b.i.d.) + A (1 g b.i.d.) ×5 day E (20 mg b.i.d.) + C (500 mg b.i.d.) + M (500 mg q.d.) ×5 day | 140 | 72.1 | 76.5 |

q.d., once daily; b.i.d., twice daily; q.i.d., four times daily; E, esomeprazole; L, lansoprazole; C, clarithromycin; A, amoxicillin; Lev, levofloxacin; M, metronidazole; ITT, intention to treat; PP, per protocol.
therapy in the Maastricht IV/Florence consensus report [38]. In Western countries, resistance to levofloxacin was low [65, 68, 69], and it was found that levofloxacin triple therapy could effectively eradicate *H. pylori* in these countries [65, 70–72].

However, the prevalence and the rate of antibiotic resistance of *H. pylori* in China are quite different from those in Western countries. A positive association between the resistance to levofloxacin and the resistance to clarithromycin was found in China [26]. Qian et al. reported that the ITT eradication rate of *H. pylori* after 7 days of levofloxacin triple therapy as a first-line therapy was only 78.1% in Nanjing, which is unacceptable [40]. When used as a second-line therapy, levofloxacin-containing therapy produced an even lower ITT eradication rate of 66.2%, as reported by Gu et al. [73].

Levofloxacin triple therapy should not be recommended as an empirical therapy in China because of the high antibiotic resistance that is present. Fluoroquinolone therapy was highly effective only when fluoroquinolone resistance rates were <12% [74].

**Rescue therapy**

As previously mentioned, levofloxacin-containing therapy may not suitable in China, bismuth-containing quadruple therapy was recommended by the fourth Chinese *H. pylori* consensus report. If the initial therapy fails, another regimen can be selected as a rescue therapy [18].

As Graham DY reported, “Quadruple rescue treatment, containing bismuth and furazolidone, is our pièce de résistance, and we have had essentially no failures in the USA even after multiple prior treatment failures” [4]. A retrospective study showed that after 14 days of treatment with a quadruple regimen (furazolidone, amoxicillin, and bismuth citrate in combination with proton-pump inhibitors), an *H. pylori* eradication rate as high as 90.35% (206/228) (according to ITT analysis) could be achieved after previous treatment failures [75].

Recently, rifabutin-containing regimens used as a rescue therapy were assessed in Australia, and they produced a high eradication rate [76]. However, this therapy may increase the risk of resistance to tuberculosis treatments [77], which may have serious consequences, especially in China, a nation with a high prevalence of tuberculosis.

**Adjuvant therapy with probiotics**

Because increases in resistance and side effects occur as a result of the use of routine antibiotics, research on adjuvant therapy with probiotics is the frontier of *H. pylori* eradication. Many studies and meta-analyses that have recently been published have shown that adjuvant probiotic therapy could improve the *H. pylori* eradication rate and that, when combined with routine therapy, it could reduce the side effects of antibiotics [78–81]. All of these data imply that adjuvant therapy with probiotics may have promising effects; therefore, large-sample, multicenter, randomized controlled studies should be performed in the future to determine the efficacy of this therapy.

**Conclusions**

The prevalence of *H. pylori* infection has declined in the past decade, but it has nevertheless remained at a high level. In clinical practice, clinicians should follow the rule, “Treat everyone who tests positive—do not test if not intending to treat,” with respect to *H. pylori* infection in developing countries, as stated by the World Gastroenterology Organisation Global Guidelines [82]. Resistance to clarithromycin, metronidazole, and levofloxacin is high in China, whereas resistance to amoxicillin, furazolidone, and tetracycline is rare. Clinicians should choose a regimen associated with low antibiotic resistance and with a high eradication rate in their particular region. Standard triple therapy should not be recommended in most area in China. Bismuth-containing quadruple therapy could reach an good eradication rate, both for primary therapy and rescue therapy. The efficacy of new therapeutic regimens for *H. pylori* should be studied in the future.

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**Author contributions**

Xie C and Lu NH contributed equally to the review and writing of this paper.

**References**

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