

# Mistakes in the management of *Helicobacter pylori* infection and how to avoid them

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The sequelae of *Helicobacter pylori* infection, a known Group 1 carcinogen, can lead to significant morbidity and mortality worldwide. Billions of people are infected with *H. pylori*, but the incidence of *H. pylori* infection is declining in many parts of Europe, with a study from the Netherlands showing a decline in seroprevalence from 48% in subjects born between 1935 and 1946 to 16% in those born between 1977 and 1987.<sup>1</sup> In recent years, however, eradication rates for *H. pylori* treatment have been falling, which has led to a large number of patients in the community having inadequately managed infections. Most of the problems that have led to the decline in the success of eradication treatment can be easily overcome through careful practice, supported by the robust framework provided by international guidelines. Careful practice includes the correct management of dyspepsia, the appropriate use of diagnostic tests for *H. pylori*, acceptable, efficacious treatments that enable good patient compliance and adequate follow up to insure eradication has been achieved in all cases. Here, we discuss the mistakes that are made when managing patients infected with *H. pylori*. Most of the discussion is evidence based, but where evidence is lacking the discussion is based on the authors' clinical experience of more than 30 years in the field.



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evaluated the washout period necessary after long-term PPI treatment, consensus guidelines suggest discontinuing PPI for 2 weeks prior to testing.<sup>2</sup>

## Mistake 3 | Prescribing eradication treatments of inadequate duration

A key factor in the declining rates of success for *H. pylori* eradication therapies is the use of 7-day triple regimens or 10-day quadruple regimens. For all treatment regimens, 14-day courses are proven to have superior efficacy and their use has been adopted by all relevant recent consensus guidelines on the topic, including the Maastricht V guidelines, which recommend 14-day courses for all treatment regimens except when 10-day courses have been proven of equal efficacy.<sup>2</sup> In spite of this, 7-day treatment regimes are still used in many local protocols, which is most likely a legacy issue. For standard triple therapy, meta-analyses have consistently shown that 14-day courses increase cure rates when compared with 7-day or 10-day courses and the side-effect rates did not differ.<sup>4</sup> The OPTRICON trial of non-bismuth quadruple therapies showed 14 days of treatment achieved significantly higher eradication rates than either 7 or 10 days of treatment.<sup>5</sup> Other large trials of bismuth-based quadruple therapies have suggested similar efficacy for 10 and 14 days of treatment, but that longer durations are superior in areas of high metronidazole resistance. However, the findings of some studies indicate that although longer durations of therapy are associated with higher eradication rates, there may also be a higher risk of events that lead to discontinuation.

## Mistake 1 | Failing to investigate dyspepsia appropriately using 'test and treat' or 'endoscope and treat' pathways

Dyspepsia is a term used inconsistently across the literature to describe a wide range of upper gastrointestinal symptoms, from upper abdominal pain to heartburn, nausea, bloating, and retrosternal pain. The Maastricht V consensus guidelines recommend a policy of 'test and treat' for patients under the age of 45 who have dyspepsia, consisting of a noninvasive test for *H. pylori* infection followed by eradication if present.<sup>2</sup> The urea breath test (UBT)—a safe means of testing for *H. pylori* infection—is widespread, acceptable to patients and easy to perform. Stool antigen testing with validated laboratory-based monoclonal tests are equivalent to the UBT, but may be less acceptable to some patients. Serology should not be used routinely as part of the 'test and treat' approach, but may be useful when patients are known to have taken antimicrobial drugs (within 4 weeks) or antiseptic drugs (within 2 weeks) before the test, or if there is ulcer bleeding, atrophy or gastric malignancies and it may not be desirable to discontinue current medications. An 'endoscope

and treat' approach is recommended for patients who are older than 45 years of age because of the higher risk of malignancy or in patients with 'red flag' features, such as weight loss, dysphagia, overt gastrointestinal bleeding, abdominal mass and iron-deficiency anaemia (figure 1).

## Mistake 2 | Testing for *H. pylori* infection when the patient is on a PPI or antibiotics

Proton-pump inhibitors (PPIs) can be obtained over the counter without a prescription in numerous countries and generic versions of several PPIs are also available, making them widely available drugs. In addition, the efficacy of PPIs for treating pain and heartburn, means that they are frequently used to treat dyspepsia symptoms. Consequently, it is likely that a patient will be taking a PPI when they consult for dyspeptic symptoms. A PPI increases the gastric pH, leading to a decreased bacterial load and migration of the bacteria from the antrum to the corpus, which interferes with the accuracy of the diagnostic tests for *H. pylori* infection and leads to false-negative results in 10–40% of cases.<sup>3</sup> Although no study has

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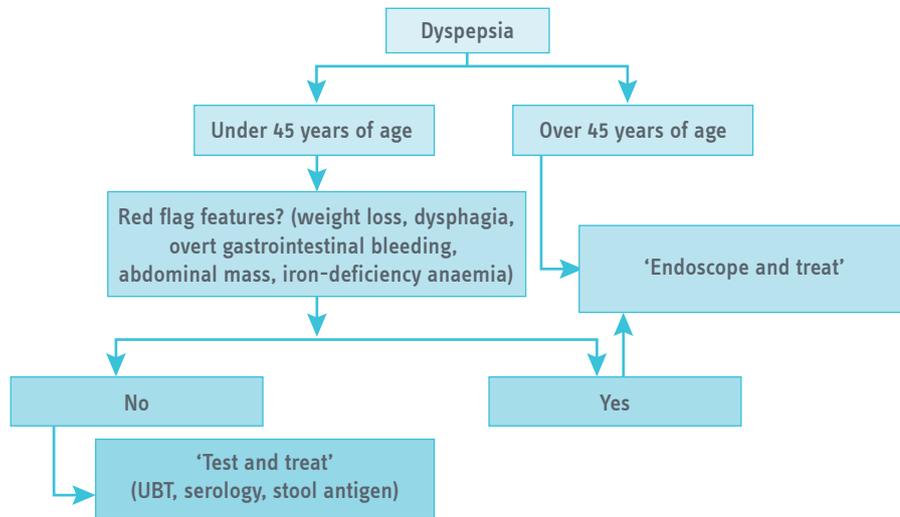


Figure 1 | The use of ‘test and treat’ versus ‘endoscope and treat’ for the management of dyspepsia. UBT, urea breath test. Courtesy of A. O’Connor.

**Mistake 4 | Not treating *H. pylori* infection for fear of aggravating reflux**

Gastro-oesophageal reflux disease (GORD) is increasing in prevalence worldwide, probably due to rising rates of obesity, and has known serious sequelae, such as Barrett oesophagus and adenocarcinoma of the oesophagus. *H. pylori* infection (especially with CagA<sup>+</sup> strains) seems to have a negative association with GORD and its sequelae. Indeed, *H. pylori* infection was shown to be present in 39% of GORD sufferers compared with 50% of controls in a review of 26 studies.<sup>6</sup> This apparently negative association has led some authorities to question whether or not *H. pylori* infection in a population is protective against GORD and whether falling rates of infection can explain the increase in rates of cancer arising from Barrett oesophagus in Europe. A meta-analysis on this topic has suggested that there is a statistically significant inverse relationship between serologic *H. pylori* positivity and Barrett oesophagus and adenocarcinoma of the oesophagus, which has led some practitioners to avoid the ‘test and treat’ strategy. However, neither of the randomized controlled trials (RCTs) of population-level screening and treatment conducted in the UK demonstrated any evidence of an increase in gastro-oesophageal reflux symptoms.<sup>7,8</sup> In addition, in the trial by Moayyedi et al., reflux symptoms were less frequent at 2 years among those assigned to eradication therapy than those who were not (22.6% versus 27.4%, *P* = 0.02).<sup>6</sup> A separate meta-analysis showed no association between *H. pylori* eradication and development of new cases of GORD in the population of dyspeptic patients although in a subset of patients with peptic ulcer disease a twofold increased risk was noted.<sup>9</sup> Given the

current evidence, and as *H. pylori* infection is a Group 1 carcinogen for gastric cancer, discontinuing the practice of ‘test and treat’ because of anxiety about a putative risk of cancer associated with Barrett oesophagus cannot be justified.

**Mistake 5 | Failing to enact public health controls against *H. pylori* infection to reduce gastric cancer incidence**

The basis of most public health measures to control cancer includes the elimination of carcinogens, and the detection and surveillance of premalignant conditions. Despite the fact that gastric cancer is a condition that has a recognized and readily treatable carcinogen, in the form of *H. pylori* infection, and a clear sequence of detectable premalignant conditions, it remains a curious anomaly that it has received neither a great deal of investment nor emphasis from most public health authorities, even though the disease is the fifth most common cancer in terms of incidence, and is the third most common cause of cancer death worldwide, responsible for almost three-quarters of a million deaths annually.<sup>10</sup>

Population screening and mass eradication of *H. pylori* is a feasible, efficacious and cost-effective means of significantly reducing the incidence of gastric cancer in those at high risk. In addition, eradication probably offers other public health benefits in terms of reducing the incidence of peptic ulcer disease and the economic burden of dyspepsia in the community. Frontline practitioners can help in this by advocating for more attention to be paid to public health measures against *H. pylori*.

**Mistake 6 | Not adequately explaining *H. pylori* infection and the need for eradication therapy to the patient (especially in an endoscopy unit) and not supporting compliance**

Compliance with therapy has a considerable influence on treatment failure and the subsequent development of antibiotic resistance. 10% of patients prescribed *H. pylori* eradication therapy fail to take even 60% of their medication and progressively poorer levels of compliance with therapy are associated with significantly lower levels of eradication.<sup>11</sup> In one study eradication levels of 96% were observed for patients who took 60% or more of their prescribed medications compared with eradication levels of 69% for those taking less than 60% of their prescribed medications.<sup>12</sup>

Factors such as therapy duration, the motivation of the prescribing physician, the quality of the information provided to the patient, the efficacy of the treatment and the associated side effects all influence treatment compliance. Frequently, in the endoscopy unit patients may be provided with prescriptions having recently been sedated and not fully understand the need for eradication therapy. A frank and in-depth conversation should be had with the patient to explain the need to comply with eradication therapy, emphasising the complications that can be associated with *H. pylori* infection and the perils of antibiotic resistance.

**Mistake 7 | Being uninformed about carcinogenic properties of *H. pylori***

The current accepted model for gastric carcinogenesis is an expansion of that first published by Correa et al. in 1975.<sup>13</sup> This model proposes that gastric cancer is the end result of a number of mutations that begin with an unknown environmental trigger in early life, now known to be infection with *H. pylori*, leading to a superficial gastritis, then chronic nonatrophic gastritis, followed by gastric atrophy and achlorhydria. Gastric intestinal metaplasia then ensues, assuming progressively more primitive forms before, finally, cell transformation occurs with the development of dysplasia and ultimately carcinoma. This model is supported by evidence from a study of individuals from communities with differing risks of gastric cancer—by the time individuals in the highest risk region were 25 years of age <25% had an entirely normal gastric mucosa. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare type of non-Hodgkin lymphoma that accounts for 12–18% of extranodal disease and has an

incidence of 1 per 100,000 population per year. Most patients who have gastric MALT lymphoma are infected with *H. pylori*, and frequently the disease can be cured by eradicating the bacterium. Knowledge of this association between *H. pylori* infection and gastric MALT lymphoma among physicians is patchy at best and has led to a failure to emphasise the importance of treatment and eradication of the pathogen. The significance of the sequelae of latent *H. pylori* infection is not always appreciated.

### Mistake 8 | Failing to retest to confirm eradication of *H. pylori*

The UBT is a valid and reliable test for evaluating *H. pylori* eradication post treatment, and testing to confirm treatment success should be performed at least 4–8 weeks after completion of *H. pylori* eradication therapy. This post-treatment confirmation of eradication is recommended in all sets of published guidelines on the topic. In spite of this recommendation, compliance with the need to retest to confirm eradication is poor—in one study retesting was observed in 62.9% of patients diagnosed in secondary care and in 53.1% of patients in primary care.<sup>14</sup> With eradication rates falling across a large number of studies it is imperative that eradication is checked and second-line therapy prescribed when necessary.

### Mistake 9 | Not surveying and monitoring resistance rates

Previously, the gold-standard treatment for *H. pylori* infection was considered to be a 1-week course of PPI triple therapy, consisting of a PPI in combination with clarithromycin and either amoxicillin or metronidazole. However, in the past 5–10 years, eradication rates achieved with 1 week of PPI triple therapy have declined to unacceptable levels, largely due to the burgeoning problem of antibiotic resistance, particularly to clarithromycin. As a result, current recommendations to improve eradication rates require knowledge of local clarithromycin resistance rates. If the rate is <20%, PPI triple therapy can still be used, although treatment should be extended to 2 weeks.<sup>2</sup> However, in regions where the resistance rate is 20% or greater, quadruple therapy should be preferred, which consists of bismuth in combination with a PPI and two antibiotics (usually metronidazole and tetracycline). In reality, few centres maintain data on antibiotic resistance rates. The development of national centres of excellence with respect to research on *H. pylori*, which

could maintain up-to-date data on antibiotic resistance rates, monitor data on malignancy and premalignant conditions and act as focal points for international research collaborations, would be desirable.<sup>15</sup>

### Mistake 10 | Inadequately evaluating for *H. pylori* infection during endoscopy

Gastroscopy is incomplete without biopsy samples being taken and *H. pylori* infection should be looked for at every endoscopy. The rapid urease test (RUT) is an inexpensive and fast method of detecting *H. pylori* infection (sensitivity and specificity >90%), which allows treatment to be prescribed at the point of care.<sup>16</sup> Taking biopsy samples from the antrum and body of the stomach and placing both tissues in the same RUT kit increases the diagnostic yield.<sup>17</sup> False-negative test results are not uncommon in the setting of PPI use, antibiotic use, bismuth use or acute gastrointestinal bleeding. In situations such as duodenal ulcer, where a high pre-test probability and index of suspicion for *H. pylori* infection exist, a negative RUT result should not be used to exclude *H. pylori* infection and alternative modalities, such as histologic evaluation of gastric tissue and culture and sensitivity testing, should be considered.

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### Your *H. pylori* briefing

#### UEG Week

- “Is mass eradication of *H. pylori* rational?” session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1578&conference=144>].
- “From guidelines to clinical practice: *H. pylori*” session at UEG Week 2016 [<https://www.ueg.eu/education/session-files/?session=1635&conference=144>].
- “*H. pylori*-associated gastric carcinogenesis” session at UEG Week 2014 [<https://www.ueg.eu/education/session-files/?session=1206&conference=76>].
- “*H. pylori*: Have we solved all problems?” session at UEG Week 2014 [<https://www.ueg.eu/education/session-files/?session=1133&conference=76>].
- “National Societies Symposia: *H. pylori* across Europe” at UEG Week 2014 [<https://www.ueg.eu/education/session-files/?session=1229&conference=76>].

#### Society conferences

- EHMSG / ESPGHAN Postgraduate Course 2015 [<https://www.ueg.eu/education/conference-files/?conference=134>].

#### Standards and Guidelines

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