







UPDATE ON HELICOBACTER PYLORI INFECTION

-  ***Helicobacter pylori* infection plays an important role in upper gastrointestinal disease**
-  **Eradication of *H. pylori* can reduce the incidence of both peptic ulcer disease and gastric cancer**
-  **Confirmation of *H. pylori* eradication should be performed at least four weeks after treatment**
-  **Causes of treatment failure include antimicrobial resistance and non-adherence to treatment**

Helicobacter pylori (*H. pylori*) is recognised as the most common chronic human bacterial infection,¹ affecting up to 50% of the world's population.² *H. Pylori* (initially called *Campylobacter pyloridis*) and its association with gastritis was first discovered in 1982.^{1,3,4} It has been said that the discovery of *H. pylori* and the realisation of its importance in upper gastrointestinal (GI) diseases represents one of the most important developments in medicine of the past century.⁵

***H. pylori* plays a crucial role in the pathogenesis of upper GI disease including gastritis, peptic ulcer disease (PUD) and gastric cancer.**^{3,6} Eradication of *H. pylori* can lead to a reduction in the occurrence of PUD and prevention of gastric cancer.^{6,7} However, in recent years there is increasing concern that the eradication treatment is failing and that there is increasing antimicrobial resistance.^{3,8}

EPIDEMIOLOGY

The prevalence of *H. pylori* infection varies between countries; in European studies the prevalence varies between 7 and 33%.⁹ Infection is usually acquired in childhood;¹ in developing countries, the infection is typically acquired before 10 years of age, while in developed countries there is an age-related increase in prevalence.^{1,2} The major risk factor for *H. pylori* infection is the socio-economic status of the family during childhood, in particular the level of sanitation and household hygiene,^{1,2,10} however genetic susceptibility also appears to play a role.¹ The predominant genotype varies greatly between regions and accounts for some of the gastric cancer risk seen in some population groups, such as Japan and South Korea which tend to harbour more virulent strains.¹ The exact route of transmission of *H. pylori* is unknown; currently favoured mechanisms appear to be gastro-oral and faecal-oral routes.¹ The role of screening and eradicating *H. pylori* in the general population and in targeted populations, as a means to reduce the incidence of gastric cancer is an area of much debate.⁹ There is growing evidence that adopting such an approach in populations at high risk of gastric cancer may reduce the future incidence of gastric cancer.⁹

PATHOPHYSIOLOGY

H. pylori is a motile, flagellated, gram-negative, spiral bacterium,¹¹ which survives the acid environment of the stomach by producing the enzyme urease.^{2,11} **Infection with *H. pylori* is a co-factor in the development of duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%) and gastric mucosa associated lymphoid tissue (gMALT) lymphoma (in <0.01%).**² Infection with *H. pylori* can lead to inflammation of the gastric mucosa with subsequent ulceration.^{1,2,11} Infection is a major cause of chronic gastritis, a condition that initiates the pathogenic sequence of events leading to atrophic gastritis, intestinal metaplasia, dysplasia and subsequently cancer.¹¹⁻¹⁴ While the bacterium is not a direct cause of cancer, its presence and resultant reduction in acid production are necessary factors in causation.¹¹ The risk of these disease outcomes in infected patients varies widely among different populations and the **great majority of patients with *H. pylori* will not have any clinically significant complications.**^{2,11}

GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD): The prevalence of *H. pylori* infection is lower among patients with GORD and those with oesophageal adenocarcinoma (which may arise as a complication of GORD) than among healthy controls.^{2,12,15,16} The nature of the negative association is unclear.^{11,12} There has been concern that *H. pylori* eradication might worsen GORD, but the current consensus is that there is no association between eradication and the development of GORD.^{2,11-12,16,17}

EXTRA-INTESTINAL DISEASE: Studies have looked at a possible role of *H. pylori* as a trigger for extra-intestinal diseases including cardiovascular diseases, neurological disorders, diabetes mellitus, ear and eye diseases, immunological and haematological disorders, liver and bile tract disease, gynaecological and respiratory pathologies.^{18,19} In general, no

conclusive evidence of a possible causal association has been found. There is, however, evidence that *H. pylori* may play a role in iron deficiency anaemia and idiopathic thrombocytopenic purpura (ITP);^{12,16,18} *H. pylori* eradication has been shown to reverse iron deficiency anaemia in patients with asymptomatic gastritis and to improve iron absorption.^{12,16} Eradication has also been shown to induce a significant platelet response in a proportion of patients with ITP.¹²

Non-invasive tests for the diagnosis of *H. pylori* infection include the C-urea breath test (UBT) and monoclonal stool antigen tests.^{11,12,20} **An accuracy of >95% for the UBT has been reported;^{3,12} this is the preferred diagnostic test for *H. pylori*** if the patient does not require an endoscopy.^{10,21} The use of serology is not recommended in clinical practice as it may remain positive up to a year after successful eradication.^{10,21} **For both the UBT and the stool antigen test, the patient should stop taking proton pump inhibitors (PPIs) and H₂ receptor antagonists for 2 weeks, and antimicrobials for 4 weeks before testing**, since these medications may suppress the infection and reduce the sensitivity of testing.^{2,12,21}

Upper endoscopy is an important diagnostic tool and is required for specific patients, including those with “alarm signals” (e.g. bleeding, anaemia, unexplained weight loss, progressive dysphagia, recurrent vomiting)^{10,22} and those who experience failure of eradication treatment. *H. pylori* infection can be detected on endoscopic biopsy of the gastric mucosa, by means of several techniques.² One such technique, the rapid urease test, can detect the presence of infection within one hour with satisfactory accuracy (>90%).¹²

INDICATIONS FOR TREATMENT

International guidelines have been published on the management of *H. pylori*, including guidelines by the European Helicobacter pylori Study Group (EHSg) which was founded in 1987.¹² Since the vast majority of patients with *H. pylori* do not have any related clinical disease, routine screening is not considered appropriate.² The Maastricht III guidelines published by the EHSg recommend indications for eradication of *H. pylori*, as listed in table 1.

Table 1: Indications for *H. pylori* treatment^{3,12}

- Non-ulcer dyspepsia “Test and treat”
- Peptic ulcer disease
- Gastric MALT
- Atrophic gastritis
- Post resection of gastric cancer
- First degree relatives of gastric cancer patients
- Patient wishes
- Unexplained iron deficiency anaemia
- Idiopathic thrombocytopenic purpura
- Patients requiring long-term NSAIDs

NON-ULCER DYSPEPSIA: Dyspepsia defines a wide spectrum of GI symptoms that affect up to 25% of the Western world sporadically.²² *H. pylori* has been found more frequently in dyspeptic patients than in controls.²² Currently a “test and treat” strategy is recommended for adult patients <50 years presenting with persistent dyspepsia,²¹ who do not exhibit any “alarm features” that require prompt endoscopy.^{10,22} *H. pylori* eradication gives some benefit in non-ulcer dyspepsia but meta-analysis has shown that 12 to 15 infected patients need to be treated to cure one patient.¹⁶ A UK study found no symptomatic advantage for *H. pylori* “test and treat” compared to proton pump inhibitor (PPI) therapy but a slight advantage in terms of cost effectiveness over a 12-month period.²³

PEPTIC ULCER: There is overwhelming evidence that the major aetiological factors in chronic peptic ulcers are infection with *H. pylori* and ingestion of non-steroidal anti-inflammatory drugs (NSAIDs).^{3,4,12,16} The first long-term clinical trial of treatment aimed at eradicating *H. pylori* in patients with duodenal ulceration was reported in 1987.^{3,5,24} This was subsequently confirmed by multiple studies and similar findings were reported for gastric ulcers.⁵ **Peptic ulcer disease (PUD) remains the strongest indication for eradication of *H. pylori*.**^{10,11,16,25} Eradication of the infection produces a long-term cure of PUD in patients whose ulcers are not associated with the use of NSAIDs.²

MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA: *H. pylori* infection has been recognised in the pathogenesis of gMALT since 1991.^{5,26} Over recent years there has been a reduction in the incidence of gMALT, which is likely related to the current decline in the prevalence of *H. pylori* infections.^{26,27} Progression of low-grade gMALT is slow and *H. pylori* eradication leads to partial or complete remission in 60-80% of patients.^{10,12,16,26} Although both gastric cancer and gMALT are complications of chronic infection, the potential interrelation is unclear.²⁶

GASTRIC CANCER: *H. pylori* is the most common proven risk for gastric cancer and **eradication is recommended to reduce the lifetime risk of gastric cancer in patients with atrophic gastritis, in patients after gastric cancer resection and in patients who are first degree relatives of patients with gastric cancer.**^{2,16} *H. pylori* was classified as a carcinogen by the International Agency for Research on Cancer in 1994.³ Even though the incidence of gastric cancer has been declining

in the USA and Western Europe over the last 50 years, the disease is still prevalent in various parts of the world and is a major public health issue.¹⁴ Globally, gastric cancer is the second most frequent cause of cancer deaths in men and the fourth among women.¹⁴ The mortality from gastric cancer has been declining steadily in Europe including Ireland^{28,29} and it was the fifth most common cause of cancer deaths in Ireland in 2007.³⁰ Gastric cancer involves the interaction of 3 major factors; the agent (*H. pylori*), the host and the external environment.¹⁴ Treatment of *H. pylori* reduces the risk for gastric cancer but does not eliminate it.^{11,12,31,32} Eradication prevents the development of pre-neoplastic changes of the gastric mucosa.¹² Currently it is thought that once pre-neoplastic changes (gastric atrophy and intestinal metaplasia) are established, prevention of further progression to invasive cancer is less likely to occur – the so-called “point of no return”.^{14,31-33}

NSAIDs: The relationship between *H. pylori* and NSAIDs is complex;^{12,16} NSAIDs independently significantly increase the risk of peptic ulcer bleeding by approximately 2 and 5-fold respectively.¹² The results of *H. pylori* eradication studies in NSAIDs users are conflicting.^{12,34,35} Eradication will effectively treat the infection but might have little impact on NSAID-related ulcers.¹⁶ Patients requiring long-term NSAIDs should be tested and treated for *H. pylori* infections.^{3,12} However eradication of the infection in patients who present with an upper GI haemorrhage does not remove the risk of re-bleeding and patients should be prescribed PPIs if they continue on NSAIDs.^{2,36}

CHILDREN: Recurrent abdominal pain in children is not an indication for a “test and treat” strategy for *H. pylori*.¹² The primary goal of a diagnostic investigation in recurrent abdominal pain should be to determine the cause of the presenting GI symptoms and not the presence of *H. pylori* infection.¹² However children with upper GI symptoms should be considered for *H. pylori* testing (after exclusion of other causes of the symptoms) and treated if they have the infection.¹²

TREATMENT REGIMENS

Various therapeutic regimens are used to treat *H. pylori* infection. First-line therapy varies in different geographical regions, depending on antimicrobial resistance and drug availability. The most commonly used initial treatment is triple therapy, which consists of a PPI plus clarithromycin and amoxicillin (or metronidazole in patients with penicillin allergy).² Recommended treatment for *H. pylori* (based on the Maastricht IV guidelines due to be published in early 2012) is summarised in table 2.^{21,37}

Table 2: Recommended treatment for *H. pylori*^{21,37*,**}

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|---|
| <p>First-line therapy</p> <ul style="list-style-type: none"> ● PPI twice daily (bd) + amoxicillin 1g bd + clarithromycin 500mg bd x 10-14 days <ul style="list-style-type: none"> ○ In cases of penicillin allergy replace amoxicillin with metronidazole 400mg bd <p>Second-line therapy (after failure of first-line therapy)</p> <ul style="list-style-type: none"> ● PPI bd + levofloxacin 500mg bd + amoxicillin 1g bd x 10 days <ul style="list-style-type: none"> ○ In cases of penicillin allergy replace amoxicillin with clarithromycin <p>Rescue therapy (after failure of second-line therapy)</p> <ul style="list-style-type: none"> ● Patients should be referred for endoscopy and treatment should be based on susceptibility testing |
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* Based on the Maastricht IV guidelines due to be published in early 2012

** Prescribers should refer to the SmPC for full details of the specific medication, including licensed indications

FIRST-LINE THERAPY: Triple therapy, as described above has been the accepted standard of care for *H. pylori* eradication since the mid 1990s.^{8,12} It may however not be the most effective first-line treatment in certain regions, due to increasing antimicrobial resistance.³⁸ There is controversy over the most effective **duration of treatment** for this regimen.³⁸ Evidence suggests that therapy is more successful if extended to >7 days,^{2,12,37-39} and many experts now recommend 10-14 days’ treatment.^{21,37} Some sources recommend that clarithromycin or metronidazole should not be used if they have been used in the previous year for any infection.⁴⁰⁻⁴² Recently there have been studies that have looked at the first-line use of other therapeutic agents (including levofloxacin and bismuth-based regimens), which have previously been used as second line therapy,⁸ however further research is required. Bismuth is no longer marketed in some countries, including Ireland.

CONFIRMATION OF ERADICATION: It is important to confirm eradication of *H. pylori*, particularly in patients who have had treatment for gMALT, or those who have undergone resection for gastric cancer,² and in patients whose symptoms persist after eradication treatment for dyspepsia.² The use of UBT or a monoclonal stool antigen test is recommended,³⁷ except in cases where repeat endoscopy is indicated e.g. gastric ulcer.¹² UBT is the best option to confirm eradication;¹² there is no role for the use of serology in eradication.³⁷ **Confirmation of eradication should be performed at least four weeks after treatment.**^{12,21}

TREATMENT FAILURE: This is an important aspect of *H. pylori* eradication. The most important predictors of treatment failure are antimicrobial resistance and non-adherence to treatment. Other factors related to eradication failure include duration of therapy, older patients, diagnosis of non-ulcer dyspepsia and smoking.^{11,43}

Antimicrobial resistance There is increasing antimicrobial resistance which has reduced the eradication rates of *H. pylori* worldwide.³ **Resistance particularly to clarithromycin (thought to be due to greater use of clarithromycin in the community for respiratory tract infections⁴⁴) is one of the most important factors in treatment failures.**^{8,12} Guidelines

recommend that in areas where clarithromycin resistance is known to be >15%, antibiotic susceptibility should be assessed before treatment is initiated.^{3,12,37} Clarithromycin resistance rates are increasing in Ireland,^{8,45} however it is currently considered an area of low resistance.³⁷ Resistance to metronidazole, which is more common than clarithromycin resistance³ is thought to be of secondary importance compared to clarithromycin in terms of eradication failure.^{8,46} Amoxicillin resistance is exceptional with some studies having a resistance rate of zero,⁸ however resistance to fluoroquinolones is increasing.^{8,37,47}

Adherence to treatment is a multifactorial process and non-adherence is a **major cause of treatment failure**.^{8,48,49} Some studies of treatment regimens suggest compliance rates of >95%, while other studies suggest that 10% of patients prescribed eradication therapy will fail to take even 60% of medicines.⁸ Adverse events, most notably diarrhoea and taste disturbance are relatively frequent with current eradication regimens, and may lead to treatment discontinuation.⁴⁹ In addition, patients may find eradication regimens complex and the importance of good compliance needs to be emphasised to patients.^{8,49} Enhanced compliance programmes are labour intensive but may be worthwhile; evidence suggests that when patients are given greater knowledge of their illness and the importance of compliance stressed, this results in significantly greater levels of both compliance and eradication.^{8,44}

SECOND-LINE THERAPY: Eradication is more difficult to achieve following a first therapeutic failure.⁴⁷ Treatment with levofloxacin, amoxicillin and a PPI has been shown to be of benefit as second-line therapy.^{3,6,8,50} There have been concerns regarding increasing resistance of fluoroquinolones, and the risk of tendonitis should also be considered.^{3,8,44} Penicillin allergy patients who require second-line therapy are a particular challenge for clinicians.⁸ A recent study found that a levofloxacin-containing regimen with omeprazole and clarithromycin gave encouraging results as second line therapy in the presence of penicillin allergy.^{8,51}

In many countries, second-line treatment with quadruple therapy containing bismuth, metronidazole, tetracycline and a PPI is recommended.^{2,3,8,40,52}

RESCUE THERAPY: Following second-line treatment failure, referral for endoscopy with culture and sensitivity testing of *H. pylori* is recommended.³ Options for rescue therapy include non-bismuth quadruple “concomitant” and sequential therapy.²¹ Concomitant therapy consists of a PPI + three antibiotics (amoxicillin, clarithromycin and metronidazole) taken for 10 days.^{8,21} The primary goal of sequential therapy, consisting of 5 days of a PPI + amoxicillin followed by 5 additional days of a PPI + clarithromycin + metronidazole, is to overcome clarithromycin resistance.^{2,8,11,21,38} **However, the main drawback with sequential therapy lies in its complexity, which may have a negative impact on compliance.**⁴⁴ Other studies have looked at sequential therapy using tetracycline in place of clarithromycin, with eradication rates of up to 82%.⁴¹

PROTON PUMP INHIBITORS (PPIs): are an integral constituent of triple therapy and are generally regarded as equivalent in efficacy.⁴⁸ Even though there are pharmacokinetic differences between the PPIs, there is no evidence of a clinically significant difference in *H. pylori* eradication rates when different PPIs are used in first-line triple therapy regimens.^{48,49} Currently in Ireland, not all PPIs are authorised for *H. pylori* eradication; prescribers should refer to the SmPC for full details of the specific medication.

SUMMARY

The management of *H. pylori* can be summarised as follows:

- **Treatment of *H. pylori* infection is recommended in patients with peptic ulcer disease, gMALT, atrophic gastritis, post-resection of gastric cancer, first degree relatives of gastric cancer patients and in response to patient wishes**
- **The recommended first-line treatment for *H. pylori* is triple therapy consisting of a PPI plus clarithromycin and amoxicillin or metronidazole**
- **A “test and treat” strategy is recommended for patients <50 years of age with dyspepsia**
- **Patients should stop taking PPIs and H₂ receptor antagonists for 2 weeks, and antimicrobials for 4 weeks before testing for *H. pylori***
- **The preferred non-invasive diagnostic test in clinical practice for *H. pylori* is the urea breath test**
- **Patients should be retested for *H. pylori* 4 weeks after eradication treatment**
- **Causes of treatment failure include antimicrobial resistance and non-adherence to treatment**
- **Referral for endoscopy should be considered for patients who experience second-line therapy failure**

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List of references available on request. Date of preparation: September 2011

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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