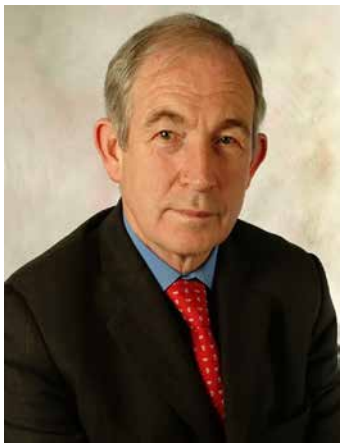
# The Helicobacter pylori revolution

***Written by Professor Colm O'Moráin, National Clinical Lead in Gastroenterology & Hepatology, RCPI/HSE***
***Emeritus Professor of Medicine Tallaght University Hospital/Trinity College of Dublin***
***Consultant Gastroenterologist, Beacon Hospital***

**Introduction**

The discovery of Helicobacter pylori (H. pylori) in 1983 by the Australian doctors Barry Marshall and Robert Warren has led to a paradigm shift in medicine.[1] The Australians were awarded the Nobel Prize for Medicine in 2005. I was fortunate to be involved in the H. pylori field from the beginning. A multi-disciplinary team comprising a microbiologist (Prof. C. Keane), pathologist (Prof. E. Sweeney) along with junior staff (G. Coughlan, H. Humphries, D. Gilligan and D. McKenna) in the Meath and Adelaide Hospitals and Trinity College Dublin first described, in the Lancet in 1987, that eradication of H pylori cured duodenal ulcer.[2] Warren and Marshall, a year later, also in the Lancet, confirmed our observation.[3] Prior to this discovery, long term acid suppression or surgery was the preferred treatment. H. pylori is the most common pathogen in the world and affects billions of people worldwide.



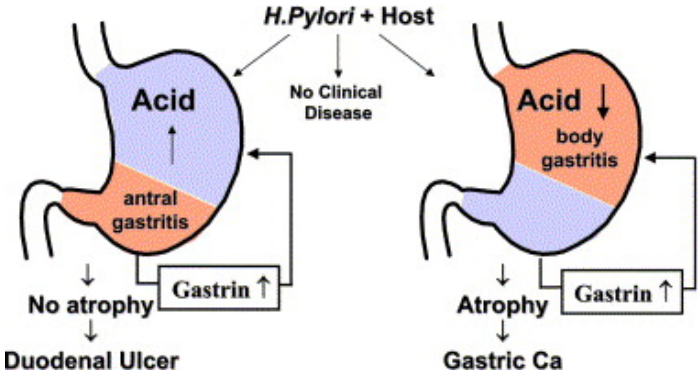
Professor Colm O'Moráin, National Clinical Lead in Gastroenterology & Hepatology, RCPI/HSE - Emeritus Professor of Medicine Tallaght University Hospital/Trinity College of Dublin - Consultant Gastroenterologist, Beacon Hospital

**Pathophysiology**

Since its discovery, *H. pylori* has been found not only to cause peptic ulcer but also gastric cancer and gastric lymphoma.[4] *H. pylori* is the most identifiable and treatable cause of non-ulcer dyspepsia. Non-ulcer dyspepsia describes patients who have dyspeptic symptoms but on endoscopy do not have an ulcer. *H. pylori*, when present, always induces an inflammatory response in the gastric mucosa. The infection is acquired in childhood and persists throughout life unless efforts are made to eradicate the bacteria. Man is the only host and the bacterium is transmitted via the oral-oral or the oral-faecal route. Parents can transmit the infection to the infant. In the underdeveloped world it is largely transmitted by the oral-faecal route due to increased intestinal transit time allowing the bacteria to survive in the environment, in combination with poorer sanitation.

When the antrum of the stomach is the predominant site of infection, this is associated with the development of duodenal ulcers. These patients have high gastrin levels which act on the parietal cell to increase acid secretion resulting in excess acid production (Figure 1). In contrast, patients who have a pan gastritis (affecting both antrum and body), will develop atrophy of the gastric mucosa predisposing to the development of intestinal metaplasia and subsequent dysplasia and gastric cancer.[5] Gastric cancer usually occurs in the 7th or 8th decade which gives the opportunity to intervene.[6] This has given rise to public health initiatives to screen for and treat *H. pylori* before the above cascade begins. These initiatives have been performed in countries with high incidence of gastric cancer, such as China, Taiwan and Japan. Even in Europe there are certain areas with a high incidence of gastric cancer, such as the Baltic States (Estonia, Latvia, and Lithuania). I am involved in a pilot study to investigate whether screening and treating H pylori reduces gastric cancer mortality.[7]

Figure 1




**Diagnosis**

The diagnosis of *H. pylori* can be made invasively (Endoscopy) or non-invasively (Urea breath test, stool antigen test). Most guidelines recommend a 'test and treat' approach to patients with dyspepsia.[8] Endoscopy is reserved for patients over the age of 55 or those with alarm symptoms (weight loss, melaena, anaemia, and dysphagia). The European society of Gastrointestinal Endoscopy (ESGE) recommend taking biopsies from the antrum, incisura and body to assess the topography of the gastritis and to determine if there are subtle changes in the mucosa relating to the cascade of gastric carcinoma.[9] Biopsies can also be taken for culture and sensitivity. The rapid urease test (CLO test) is based on an enzyme secreted by the bacteria (urease) which changes the pH and colour of a media which the biopsies are placed in and give a result before the patient leaves the Endoscopy suite. This test is improved by taking a biopsy from both the antrum and the body, however it can be influenced by PPI therapy and the presence of blood. The urea breath test to detect the presence of

Helicobacter is dependent on the urease activity of the bacteria. In this test the fasting patient ingests radio-labelled C13 urea and if the bacterium is present it will split the ingested urea to ammonia and CO2. The CO2 is absorbed and excreted in the breath. The stool antigen test detects the presence of the bacteria in a stool sample. For these tests to be reliable it is important that patients are off PPIs for at least 2 weeks and if testing for success

of treatment should be delayed for 4-8 weeks post eradication therapy. New developments in molecular techniques may give rise to an accurate antibiogram which could be used to determine a personalised approach to treatment.

**Treatment**

The treatment used at the outset involved Bismuth which is a mucosal protective agent which also has antibacterial properties. There have been significant improvements in treatment since 1987 but continues to involve several antibiotics. The advent of proton pump inhibitors (PPIs) made a significant contribution to the treatment of H pylori. Treatment from the outset has been empirical and not based on culture and sensitivity. The current treatment regimen of *H. pylori* has evolved to the current triple therapy which involves three drugs twice a day for two weeks. The recommended first line therapy in Ireland consists of a PPI, Amoxicillin and Clarithromycin. This treatment initially demonstrated an efficacy of >80%. However, more recently treatment has not been as effective. There are several explanations for the decrease in efficiency of triple therapy; compliance, high gastric acidity, high bacterial load and bacterial strains that are resistant to clarithromycin.

**Compliance**

Patients should have the treatment explained to them by a healthcare profession as failure to complete a course of treatment will more than likely result in resistant strains evolving. Compliance with therapy has been identified as the single most important factor in *H. pylori* eradication. Poorer levels of compliance with therapy are associated with significantly lower levels of eradication. Numerous factors can contribute to achieving good levels of compliance. These include the complexity and duration of treatment. It is also important that the physician is motivated to ensure eradication is confirmed and the patient is sufficiently informed to empower him or her to achieve high levels of compliance. Compliance is also contingent on medication regimes that are simple, safe, tolerable and efficacious. The opportunity to improve compliance exists at every point of contact between the patient and the medical services. Experts and opinion leaders in the field can play a role by ensuring that physicians are educated and motivated enough to encourage and support compliance with *H. pylori* eradication therapy. Both patients and physicians need to be aware of the importance of the bacterium in causing disease. The importance of the doctor patient relationship is paramount. Pragmatic strategies that may be of assistance may come in the form of poly pills, combined Blister Packs, adjuvant therapies and modified release compounds. Colleagues such as pharmacists and nurse specialists can also play an important role and should be actively engaged. Structured aftercare and follow up offers the best chance for ensuring compliance and subsequent eradication of the *H. pylori* pathogen.[10]

**Resistance**

The European Medicines Agency (EMA) provides recommendations in treating bacterial infections in terms of resistant rates. A rate of resistance <10% would suggest antibiotic susceptibility with inconsistent susceptibility between 10-15%. As resistance rates rise above 15% susceptibility rates fall below acceptable levels. In terms of *H. pylori* treatment, a threshold of 15% was therefore agreed upon to define regions of high and low Clarithromycin resistance. Recent resistance rates in Ireland would suggest this figure of 15% has been surpassed and questions the ongoing use of Clarithromycin as first line therapy. For any successful eradication treatment can be predicted if the cure rate for susceptible and resistant strains is known.

Antimicrobial resistance is based on culture using gradient susceptibility testing and Agar dilution methods. These phenotype assays offer the opportunity to assess minimal inhibitory concentrations (MIC) of the antibiotics. More recently, different polymerase chain reaction (PCR) tests have been developed for clarithromycin and levofloxacin. These techniques allow assessment of point mutations responsible for antibiotic resistance. Molecular techniques are faster and can be used in smaller laboratories. Another advantage is that it is being developed for assessment of antibiotic sensitivity in stool samples. Although ideal, some studies have evaluated the cost effectiveness of susceptibility guided treatment and have achieved contradictory results. The evidence is limited to support the generalised use of susceptibility guided therapy for H pylori eradication in routine clinical practice. It is recommended that susceptibility rests are performed routinely even before first line therapy in reference centres with an interest in H pylori management. The most successful treatment should be based on sensitivity testing on cultured samples from individual patients.[11] While individualised culture based treatment for most remains aspirational, its use is increasing in reference centres who manage complex multi-drug resistant cases. Empirical therapy remains the standard of care for most treating *H. pylori*.

**Triple Therapy**

If Clarithromycin is to be employed, and the patient has a sensitive strain, the duration of therapy should for 14 days. Triple therapy would involve Clarithromycin 500mg twice a day (BD), and Amoxicillin 500mg four times a day (QID) to ensure adequate minimal inhibitory concentration (MIC) levels. Esomeprazole 40mg BD should be given to ensure maximal acid suppression. The antibiotics are taken after food but Esomeprazole should be given in the fasting state, first thing in the morning and 12 hours later to ensure maximal efficacy (proton pump most active in fasting state). Esomeprazole or Rabeprazole are the preferred PPI in Europe as the prevalence of PPI extensive metabolisers is high. *H. pylori* is more likely to be in a non replicative state when gastric pH is low (pH 3-6). By raising the pH, bacteria enter the replicative state and become more susceptible to antibiotic therapy.

**Quadruple Therapy**

The preferred first line treatment in Ireland would be Bismuth-based quadruple therapy including Bismuth, Metronidazole, Tetracycline and Esomeprazole (Figure 2). Bismuth has made a comeback as it has antibacterial properties and may assist in overcoming Metronidazole resistance. Metronidazole resistance in H pylori treatment has previously been recognised in the Irish population. However, we know that Metronidazole resistance in vitro may not correlate to the in vivo state as it can be overcome by higher

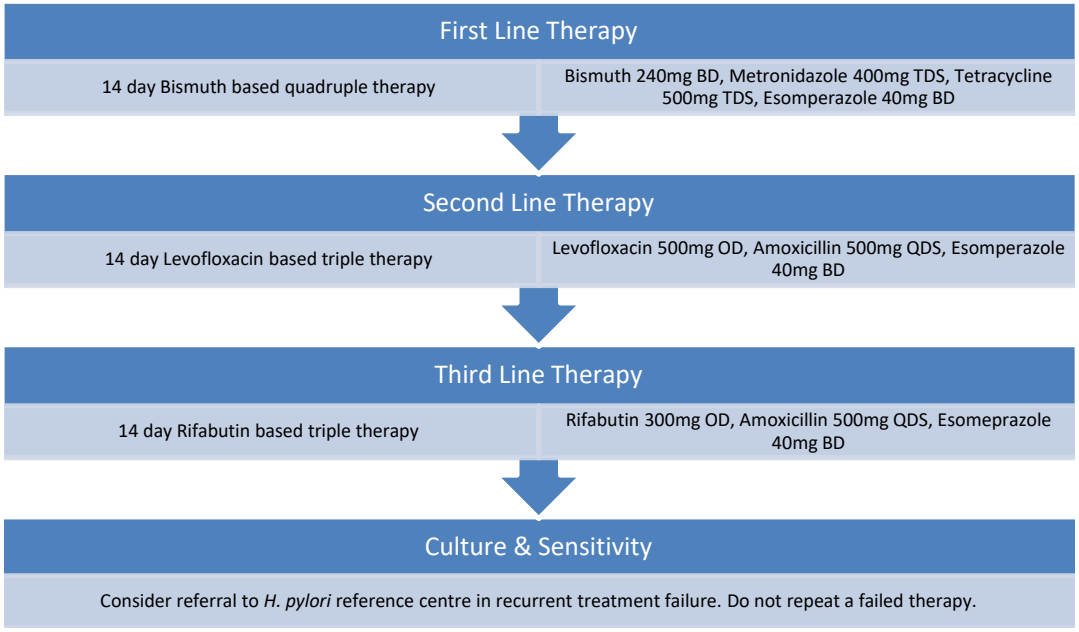



Figure 2

doses (400mg TDS) and for longer duration of treatment (2 weeks). This treatment regimen has until now been limited by the availability of Bismuth in Ireland; however this has improved more recently. Tetracycline is given at a dose of 500mg three times a day. Together this regimen has achieved eradication rates of over 90%. If Bismuth is not available, an alternative antibiotic such as Amoxicillin can be substituted.

### Rescue Therapy

Should the first line treatment be unsuccessful, a fluoroquinolone based triple therapy should be considered. It is important not to use the same treatment regimen again as it is likely to be unsuccessful due to acquired antibiotic resistance. Recent findings indicating that fluorquinolones such as Levofloxacin, or more recently Moxifloxacin or Sitafloxacin, seem to be efficacious alternatives to standard triple or quadruple therapy and may be used as rescue regimens.[12] Levofloxacin has remarkable in vitro activity against the bacteria. Moreover, Levofloxacin retains its activity in vitro when H pylori strains are resistant to Clarithromycin and Metronidazole. These encouraging results have been confirmed in vivo showing most patients with dual resistance are eradicated with Levofloxacin containing regimes. The European Pharmacovigilance Risk Assessment Committee (PRAC) recently assessed the impact of irreversible longstanding disabling reactions affecting the nervous and musculoskeletal system and the impact this might have on the benefit risk ratio of this drug group. It is recommended not to use fluorquinolones for the treatment of mild or self limiting infections and to use them only when recommended antibiotics are not effective or not tolerated. However, the recommendation is to use Levofloxacin only as a rescue therapy when first line treatment has failed. It is important to recognise that H. plyori is a chronic infection that triggers serious complications such as peptic ulcer, possibly with complications such as haemorrhage or gastric cancer. H pylori resistance to Levofloxacin is increasing and it is important to monitor this. The recommended dose of Levofloxacin in rescue triple therapy is 500mg daily combined with Amoxicillin 500mg QID and Esomeprazole 40mg BD.

Rifabutin is an antibiotic commonly used to treat Mycobacterium Avium and Mycobacterium Intercellulare in human immunodeficiency virus (HIV) infected patients. The in vitro sensitivity of *H. pylori* is high and does not share resistance to Clarithromycin, Metronidazole or Levofloxacin.[13] Resistance is only found when high doses are used for the extended duration of time that is required for the treatment of Mycobacterium. Resistance rates of *H. pylori* to Rifabutin are very low. A recent meta-analysis of Rifabutin, Amoxicillin and PPI used as rescue treatment reported an eradication rate of 83%.[14]

### Side Effects of Treatment

Side-effects of treatment can occur but are usually transient and mild. Patients should be counselled in advance about these potential side effects but encouraged to complete the course of treatment. Some of these side effects can be overcome by the addition of a probiotic. A transient increase in antibiotic resistance to certain bacteria is observed immediately after treatment. However the susceptibility to the antibiotic is restored to the basal state within 2 months after H pylori eradication treatment. There is a significant short term perturbation of gut Microbiota after H pylori eradication. However the diversity of the gut Microbiota is fully restored several months after eradication therapy is complete.[15]

### European Helicobacter Registry

The European Helicobacter Registry (HPEU) was established in 2013 under the guidance of Professor Javier Gisbert and by a scientific committee on which I serve. The HPEU Registry brings together information of real clinical practice of 30 European countries including Ireland.[16] Over 30,000 patients are registered. The most recent publication from the HPEU shows the management of H pylori is extremely heterogeneous across Europe with over 100 different 1st line regimens employed (17). Triple therapy prescriptions have decreased to less than 50% especially in regions with high clarithromycin resistance. Over 90% eradication rates were observed with 14 day quadruple therapy. From 2013 to 2018 the observed shift to longer treatment duration, higher acid inhibition and better compliance increased the effectiveness of treatment. The most common errors observed are the persistence with standard triple therapy when it is ineffective, treatment duration of only 7-10 days, low dose PPI, and repeating ineffective treatment regimens, and not to emphasise compliance or to check eradication success post treatment. The current national coordinator for Ireland is Professor Sinead Smith (SMITHSI@tcd.ie).

### European Helicobacter and Microbiota Study Group (EHMSG)

The European Helicobacter and Microbiota Study Group (EHMSG) formed in 1987, of which I was a founding member. We have developed guidelines on who, how and when to treat patients with Helicobacter pylori infection. The most recent addition Maastricht V, the fifth in the series, was published in Gut in 2016 and was the most cited paper in that year.[8] Currently the 6th Maastricht consensus guidelines are being formulated and should be published later this year.

### Future Trends

Acid suppression is a fundamental component of eradication therapy. The more potent and longer duration of acid suppression results in high rates of eradication. A new innovative approach to reduce gastric acid secretion further has been the introduction of the H+K+ATPase blockers called potassium competitive acid blockers (P-CABs), which block the potassium exchange channel of the proton pump resulting in a very fast competitive reversible inhibition of acid secretion.[18] A P-CAB offers a very rapid and greater elevation of intragastric pH compared to standard PPIs. These drugs have been approved in the Asia-Pacific region with promising results. Data from trials in the Asia-Pacific region show that Vonaprazan-based triple therapy was superior to PPI based standard triple therapy.[19] This represents an exciting prospect.

A vaccine against Helicobacter pylori would be a powerful tool for preventing gastric adenocarcinoma. However, notwithstanding a proof-of-concept that vaccination can protect children from acquisition of *H. pylori* infection, there are currently no advanced vaccine candidates with only a single vaccine in Phase I clinical trial.[20] Further, the development of a vaccine against *H. pylori* is not a current strategic priority of major pharmaceutical companies despite the large global disease burden.

### Conclusion

Helicobacter pylori remains a major public health concern. Screening could be considered for detection, eradication and prevention of further serious complications. Treatments have evolved and need to be informed by local resistance rates. Compliance is a key component of treatment success and should be emphasised. The treatments outlined above will result in better eradication rates if correctly adhered to.


**References**

1) Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; 1: 1311-1315.
2) Coghlan JG, Humphries H, Dooley C. et al. Campylobacter pylori and recurrence of duodenal ulcers— a 12-month follow-up study. Lancet 1987; 330; 8568: 1109-1111.
3) Marshall BJ, Warren JR, Blincow ED et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of campylobacter pylori. Lancet 1988; 332 ; 8626–8627: 1437-1442.
4) Kuipers EJ. Helicobacter pylori and the risk and management of associated diseases: gastritis, ulcer disease, atrophic gastritis and gastric cancer. Alimentary Pharmacology & Therapeutics 1997; 11: 71-88
5) Correa P. Helicobacter pylori and gastric carcinogenesis. The American Journal of Surgical Pathology. 1995 ;19 Suppl 1:S37-43.
6) O'Connor, A., O'Morain, C. & Ford, A. Population screening and treatment of Helicobacter pylori infection. Nat Rev Gastroenterol Hepatol 14, 230–240 (2017).
7) Leja M, Park JY, Murillo R, et al. Multicentric randomised study of Helicobacter pylori eradication and pepsinogen testing for prevention of gastric cancer mortality: the GISTAR study. BMJ Open 2017; 7.
8) Malfertheiner P, Megraud F, O'Morain CA on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30
9) Pimentel-Nunes, P, Libânio, D, Marcos-Pinto, R. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019; 51(04): 365 – 388
10) O'Connor JPA, Taneike I, O'Morain C. Review: Improving compliance with Helicobacter pylori eradication therapy: when and how? Therapeutic Advances in Gastroenterology. September 2009:273-279.
11) Gisbert JP. Empirical or susceptibility-guided treatment for Helicobacter pylori infection? A comprehensive review. Therapeutic Advances in Gastroenterology. January 2020.
12) Gisbert JP. Optimization Strategies Aimed to Increase the Efficacy of Helicobacter pylori Eradication Therapies with Quinolones. Molecules. 2020; 25(21):5084.
13) Gisbert JP. Rifabutin for the Treatment of Helicobacter pylori Infection: A Review. Pathogens. 2021; 10(1):15.
14) Gingold-Belfer, R., Niv, Y., Levi, Z. et al. Rifabutin triple therapy for first-line and rescue treatment of Helicobacter pylori infection: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology 2020.
15) O'Connor, A, Furuta, T, Gisbert, JP, O'Morain, C. Review – Treatment of Helicobacter pylori infection 2020. Helicobacter. 2020; 25(Suppl. 1):e12743
16) McNicholl, AG, O'Morain, CA, Megraud, F et al. As Scientific Committee of the Hp-Eureg on Behalf of the National Coordinators. Protocol of the European Registry on the management of Helicobacter pylori infection (Hp-EuReg). Helicobacter. 2019; 24:e12630.
17) Nyssen OP, Bordin D, Tepes B On behalf of the Hp-EuReg Investigators, et al. European Registry on Helicobacter pylori management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut 2021; 70: 40-54.
18) O'Morain, NR, Dore, MP, O'Connor, AJP, Gisbert, JP, O'Morain, CA. Treatment of Helicobacter pylori infection in 2018. Helicobacter. 2018; 23(Suppl. 1):e12519
19) Shinozaki S, Kobayashi Y, Osawa H et al. Effectiveness and Safety of Vonoprazan versus Proton Pump Inhibitors for Second-Line Helicobacter pylori Eradication Therapy: Systematic Review and Meta-Analysis. Digestion 2020.
20) Sutton P, Boag JM. Status of vaccine research and development for Helicobacter pylori. Vaccine 2019; 37; 50: 7295-7299.