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Mini-Review

Management of *Helicobacter Pylori* Infection

Jemilohun A.C[1*] and Otegbayo J.A[2]

[1]*Department of Medicine, Gastroenterology Unit, Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso , Oyo State, Nigeria.*

[2] *Department of Medicine, College of Medicine, University of Ibadan and University College Hospital, Ibadan,*

ABSTRACT

Substantial progress has been made in identifying the roles *Helicobacter pylori* (*H. pylori)* play in the pathogenesis of diseases that present clinically as dyspepsia, such as chronic gastritis, gastric ulcer, duodenal ulcer, gastric carcinoma, gastric mucosal associated lymphoid tissue (MALT) lymphoma, since its discovery by Warren and Marshall in 1982. This review aims at outlining the various diagnostic and therapeutic options available to the clinician in the management of *H. pylori* infection with an appraisal of their strength and weaknesses. Relevant literatures on diagnosis and treatment of *H. pylori* infection in texts and journals were reviewed. Extensive internet literature search was made through Google, Pubmed and HINARI. Effective diagnostic and multiple antimicrobial therapies are now available, although reliable antimicrobial monotherapy has been elusive. There is increasing resistance to the first line multiple antimicrobial therapies thereby necessitating a multistage approach to the management of the infection. Of note is the relatively new sequential therapy which has an eradication rate greater than 90%. Since an ideal therapy ought to be short and should lead to an eradication rate of the organism greater than 90%, the sequential therapy seems to have a potential of becoming the standard first-line treatment for *H pylori* infection in the interim, while search is being made for the ideal antimicrobial monotherapy.

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Keywords*: Helicobacter pylori*, Dyspepsia, Gastric cancer, Gastric Ulcer, Duodenal ulcer

INTRODUCTION

Since the discovery of *H. pylori* by Warren and Marshall in 1982 (Suerbaum and Michetti, 2002), it has been evidently demonstrated that the organism plays a major role in the aetiopathogenesis of several upper gastrointestinal diseases which present as dyspepsia (Malfertheiner *et al*., 2007; Suerbaum and Michetti, 2002). This discovery has generated enormous international interest in research on the organism such that approach to investigation and treatment of patients with dyspepsia continues to evolve.

Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country (Suerbaum and Michetti, 2002). The prevalence of the infection is related to age, socioeconomic class, and country of origin (Rowland et al., 2006). A prevalence of 20-50% is reported in the adult population in the developed world but it is far higher in developing countries with prevalence as high as 90% in some countries (Graham and Sung, 2006; Suerbaum and Michetti, 2002; Holcombe, 1992). Prevalence is higher in regions of low socioeconomic and poor sanitary conditions and in rural as contrasted to urban areas. The major marker for risk of the infection is the socioeconomic status of the family during childhood (Malcolm *et al*., 2004; Malaty and Graham, 1994). In the developed countries there is an age-related increase in prevalence which is a reflection of a birth cohort effect (Malaty and Graham,

*Corresponding author:

E-mail: *chrislohun2010@hotmail.com*

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1994). It is believed that infection takes place mostly in childhood and the rate of acquisition has reduced with improved sanitary condition and probably antibiotic use in children. The primary mode of transmission is person to person and clusters are found in families. This can be through faeco-oral, oral–oral, and gastro-oral (via vomitus, gastric secretions and improperly disinfected endoscopes). Transmission could also be from water (Brown, 2000).

H. pylori is a slow–growing, microaerophilic, highly motile, gram negative spiral organism. It is 0.5 to 8.0µm wide and possesses multiple ensheathed flagella at one end (Suzuki *et al*., 2003). It has the capability of dual existence in bacillary and coccoid forms (Saito *et al*., 2003). The bacillary form is motile while the coccoid form is non-motile. The *genome* of the organism codes for about 1,500 proteins (Suerbaum and Michetti, 2002).

Bacterial aetiology of dyspepsia has been disputed in the past because of the understanding that the stomach is unfavourable to bacterial growth due to its high acid content. *H. pylori*, however, is able to overcome this by means of virulence factors which enhance colonization of the gastric epithelium and induction of tissue damage. *H. pylori* infection has been implicated in the aetiopathogenesis of chronic gastritis, gastric and duodenal ulcers, gastric carcinoma, and gastric mucosal associated lymphoid tissue (MALT) lymphoma (Graham and Sung, 2006; Suerbaum and Michetti, 2002). Prior to the discovery of *H. pylori* by Warren and Marshall in 1982 (Marshall, 1988), the hyperacidity theory held sway in the aetiopathogenesis of peptic ulcer disease. Since its discovery however, approach to management of patients with dyspepsia continues to evolve such that PUD and MALT lymphoma are now being considered as infectious diseases in which elimination of the causative agent cures the conditions (Talley and Vakil, 2005).

Although effective antimicrobial monotherapy has been elusive, effective multiple therapies are now available for the eradication of the infection (Suerbaum and Michetti, 2002). This approach, if properly implemented will reduce the expenses incurred by patients who seek medical help and hence exert a positive effect on the national economy, since dyspepsia is often a recurrent ailment (Logan and Delaney, 2001).

DIAGNOSIS OF *H. PYLORI*

There are various diagnostic tests for *H. pylori* which can be broadly classified into invasive and non-invasive tests (Malfertheiner et al., 2007; Chey and Wong, 2007). Invasive tests utilize endoscopic gastroduodenal biopsy samples while the non-invasive tests do not (Malfertheiner *et al*., 2007; Chey and Wong, 2007; Samarbaf-Zadeh *et al*., 2006).

Although most of the commonly employed tests have good sensitivity and specificity, determination of gold standard has been difficult since none of them is perfect (Cutler *et al*., 1995). Selection of the appropriate diagnostic test depends on the clinical setting. (Chey and Wong, 2007; Talley and Vakil, 2005; Suerbaum and Michetti, 2002)

NON-INVASIVE TESTS

They are the preferred means of detecting *H. pylori* infection in patients with dyspepsia who do not need oesophagogastroduodenoscopy (OGD) evaluation.

Urea breath test (UBT): It is an indirect method of detecting presence of *H. pylori* in the stomach premised on the ability of *H. pylori* to produce the urease enzyme. UBT is now being considered as the gold standard by some researchers (Romagnuolo *et al*., 2002). It is also a reliable means of evaluating the success of antimicrobial therapy in clinical practice. It is not as expensive as endoscopy.

False positives results can occur when there is bacterial overgrowth of urease-producing organisms. False negative result can also occur with recent use of antibiotics, bismuth preparations or acid suppression therapy due to their effect on the colony size of *H. pylori*.

Serology: Chronic *H. pylori* infection elicits a circulating antibody response that can be quantitatively measured by Serological assay technique like enzyme-linked immunosorbent assay (ELISA) (Monteiro *et al*., 2001). Although tests for IgG, IgA and IgM antibodies can be done, only IgG antibody test is reliable. It involves the use of serum or plasma, and lately tests on whole blood have evolved (in office test) (Vaira *et al*., 1999). Serology, because of its easy availability, affordability, and simplicity, is widely utilised in epidemiological study of *H. pylori* infection. Its major drawback is that it cannot differentiate current infection from previous exposure because it may still be positive several months after *H. pylori* eradication. Hence, they are generally not useful to confirm cure after antimicrobial therapy. It is however, useful for the initial diagnosis of *H. pylori* infection and in large epidemiological surveys (Monteiro *et al.*, 2001).

Stool antigen test (SAT): This is a relatively new form of non-invasive diagnostic test based on detection of *H. pylori* antigen in the stool. *H. pylori* adhering to gastric epithelium in infected individuals appear in their stool as a result of normal shedding of the epithelium. This implies that detection of these antigens is a direct test

of active infection which gives it an advantage over serology. SAT is an enzyme immunoassay test which is available in both polyclonal and monoclonal forms. The monoclonal immunoassay is newer and more sensitive and specific than the polyclonal assay (Koletzko *et al.,* 2003) and may be considered as an alternative to UBT in the initial diagnosis of patients with dyspepsia who do not require immediate endoscopy (Andrews *et al*., 2003). SAT is simple and relatively cheap. It can be carried out in most routine laboratories.

SAT is slightly less reliable when used soon after the end of *H. pylori* eradication therapy, and it is now generally recommended to wait for about 12 weeks to reliably confirm eradication (Matysiak-Budnik and Megraud, 2006; Koletzko *et al.,* 2003). Also, its diagnostic accuracy is impaired by proton pump inhibitors (PPI) and gastrointestinal bleeding (van Leerdam *et al*., 2003). A major drawback is related to the inconvenience of stool handling.

Other non-invasive tests which are not routinely used for diagnosing *H. pylori* include stool PCR, Urine antibody test (urinelisa) and Saliva antibody test (Miwa *et al.,* 1999; Makristathis *et al.,* 1998).

INVASIVE TESTS

Invasive tests are general used when a patient with dyspepsia requires OGD evaluation either because of alarm symptoms or treatment failure.

Rapid urease test (RUT): This also utilises the action of the urease enzyme which is produced by *H. pylori*. Gastric biopsy is placed in a medium which contains urea and a *pH* indicator. The urease breaks down the urea to produce ammonia that increases the pH of the medium which leads to a colour change. RUTs have specificity and sensitivity of greater than 90%, but false-positive results do occur (Graham and Sung, 2006). It can be performed and read within minutes to few hours in the endoscopy suite. The comparative advantage of the test to histology lies in its rapidity, simplicity and inexpensiveness.

Histology: Usually required when RUT is negative or when there is need to evaluate the gastric mucosal for gastritis, atrophy, or intestinal metaplasia (Logan and Walker, 2001). Biopsies are obtained from the gastric antrum and corpus (Ola *et al*., 2006). Several levels of each biopsy are routinely stained with haematoxylin and eosin (H&E) and with a special stain such as Giemsa, Warthin-Starry silver or cresyl-fast violet. The standard H&E stain is employed for determining histological chronic or chronic active inflammation (gastritis). The special stains are better at detecting the organism if small numbers of bacteria are present. An important advantage of histology is that, in addition to the historical record provided, sections from biopsies (or even additional sections) can be examined at any time (Logan and Walker, 2001). The drawbacks of the test are that it is highly observer-dependent, it takes a longer duration for result to be available, it requires specialized skills to perform and it is relatively expensive.

Culture: This is particularly useful in evaluating treatment failure cases after use of second line antimicrobial agents for detecting the antibiotic sensitivity pattern of the organism.

Multiple biopsies are usually taken from the gastric antrum and corpus to increase the yield of test due to the focal nature of inflammatory lesions produced by *H. pylori*. The specificity of the test is 100% while the sensitivity is slightly less (Ani Agatha *et al*., 1998). A major advantage of the test is that, pure growth of the organism can be obtained for proper identification and detailed studies e.g. antibiotics sensitivity, strain typing, genetic studies etc. The disadvantages of the test are that, it takes several days for result to be available; it is expensive, stringent condition for transportation to the laboratory may be difficult to fulfil.

Other invasive tests that may be used include direct microscopy of fresh gastric biopsies (Ani Agatha *et al*., 1998); polymerase chain reaction (PCR) (Roth *et al*., 2001); DNA-Enzyme immunoassay and (Vaira *et al*., 1999); and fluorescent in situ hybridization (FISH): which is particularly useful in detection of *H. pylori* clarithromycin resistance/sensitivity (Samarbaf-Zadeh *et al*., 2006).

TREATMENT

With the weight of evidence implicating *H. pylori* in the aetiology of different diseases manifesting clinically as dyspepsia, it will be appropriate for all patients with dyspepsia who are positive for *H. pylori* to undergo *H. pylori* eradication therapy (Malfertheiner *et al*., 2007; Talley and Vakil; 2005; Suerbaum and Michetti, 2002). More so, that *H. pylori* eradication has been associated with significant reduction in rate of recurrence of PUD and cure of MALT lymphoma.

Specific recommendation to treat includes patients with peptic ulcer disease and low grade gastric MALT lymphoma; patients with atrophic gastritis; first degree relatives of patients with gastric cancer; patients with unexplained iron deficiency anaemia; and patients with chronic idiopathic thrombocytopenic purpura (Malfertheiner *et al*., 2007; Chey and Wong, 2007).

One major challenge in the treatment of *H. Pylori* is the fact that no single agent is sufficient in eradicating the organism (Malfertheiner *et al*., 2007; Chey and Wong,

2007). Eradication of the organism requires combinations of antibiotics together with non-antibiotic adjunctive agents. Drugs are given in combinations of 3 (triple) or 4 (quadruple). Each regimen consists of at least 2 antibiotics. Antibiotics that are traditionally used include amoxicillin, nitroimidazole (metronidazole and tinidazole), clarithromycin, tetracycline and bismuth. Adjunctive agents include histamine-2 receptor blockers (H2RB), proton pump inhibitors (PPI), and ranitidine-bismuth citrate (RBC).

- Triple therapy: two antibiotics + one adjunctive agent.
- Quadruple therapy: two antibiotics + two adjunctive agents

Dual therapy is no longer recommended because of wide spread antibiotic resistance. Regional antibiotic sensitivity pattern should also be put into consideration in the choice of antibiotics.

Maastricht III -2007 consensus report and the American College of Gastroenterology Association (ACG) suggested two lines of therapy (Malfertheiner *et al*., 2007; Chey and Wong, 2007):

First-line therapy: e.g.

- PPI + Amoxicillin + Clarithromycin
- PPI + Amoxicillin + Metronidazole ,or
- Bismuth containing quadruple therapy.

Since failure rate is still above 20% in most commonly used first-line therapies (Gisbert *et al*., 2007), there is need for a second line therapy.

Second-line therapy (usually quadruple therapy): e.g.

- PPI + Bismuth + Metronidazole + Tetracycline
- Ranitidine + Bismuth + Metronidazole + Tetracycline
- If bismuth is not available, PPI-based triple therapy could be used.

The choice of a second-line treatment depends on the type of the initial treatment that was used. Most authorities concur that culture is not necessary after a first eradication failure in order to start the second-line therapy (Malfertheiner *et al*., 2007; Avidan *et al*., 2001). If a clarithromycin- based regimen was used, a metronidazole- based treatment (or at least a clarithromycin-free regimen) should be used thereafter, and vice versa (Battaglia *et al*., 1998). This recommendation is based on the observation that acquired bacterial resistance to clarithromycin or metronidazole is often a consequence of the previous treatment failure (Peitz *et al.*, 1999). Although, a triple regimen can be used, a quadruple therapy is the preferred regimen after initial treatment failure. (Malfertheiner *et al*., 2007; Hojo *et al*., 2001).

Another challenge in the treatment of *H. pylori* infection is the determination of the optimal duration of therapy. While there is controversy as to whether 7, 10, or 14 days is optimal (Calvet *et al*., 2008; Fuccio *et al*., 2007); it has been generally observed that longer durations provide better results than a 7 day duration (Calvet *et al*., 2005; Broutet *et al*., 2003; Fischbach *et al*., 2002). Current European and United States' recommendations also support 14 days as the duration of choice. (Malfertheiner *et al.*, 2007; Chey and Wong, 2007). Despite this, available evidence suggests that a 7-day treatment duration is sufficient when quadruple therapy is used as a second line treatment (Gisbert, 2009; Choung *et al*., 2006; de Boer *et al*., 1994).

It should be noted that the use of the quadruple therapy as the optimal second-line therapy is fraught with problems of regimen complexity and a relatively high incidence of adverse effects (Gisbert and Pajares, 2002). These result in poor compliance, failure of eradication in about 20 to 30% of patients and eventual drug resistance (Gisbert and Pajares, 2002). There is therefore a need to design drug regimens that are simple and have few side effects.

Third line or rescue therapy

To treat patients who have already undergone first- and second-line therapies is a common challenge because of the risk of development of double antibiotic resistance (Megraud, 2004). Although, various therapeutic protocols have been tested by different groups (Gisbert, 2009; Malfertheiner *et al.*, 2007) a standard third-line therapy is currently lacking.

When available, endoscopic biopsy culture and antibiotic sensitivity testing is the most suitable option for patients with two eradication therapy failures (Gisbert, 2009; Malfertheiner *et al*., 2007). The third-line therapy should avoid metronidazole and clarithromycin and antibiotics that are likely to have contributed to development of resistance

Other classes of antibiotics have emerged in the treatment of *H. Pylori* i. These include-fluoroquinolones like levofloxacin, Gatifloxacin and Moxifloxacin; rifabutin; and furazolidone (Gisbert, 2009; Malfertheiner *et al*., 2007; Graham and Sung, 2006). They are usually deployed to replace clarithromycin and metronidazole in rescue therapies and in first or second line regimens.

Levofloxacin: levofloxacin has been established as an alternative to standard antibiotics not only in first-line therapies but also in 'rescue' regimens (Saad *et al*., 2006; Gisbert and Pajares, 2005). Levofloxacin-based 'rescue' regimens have been found to have an

eradication rate of 80% (Gisbert and Morena, 2006). A major drawback to this encouraging finding is the fact that *H. pylori* resistance to quinolones is easily acquired, and in countries with a high consumption of these drugs, the resistance rate is already relatively high (Carothers *et al*., 2007; Graham and Sung, 2006).

Rifabutin: Rifabutin-based rescue therapy is an encouraging treatment strategy following multiple preceding eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, and tetracycline (Leung and Graham, 2002). Rifabutin has an important side effect of myelotoxicity (Canducci *et al*., 2001). It must be used cautiously because it can select resistance among Mycobacteria species. *H. pylori* resistance to it may also occur but it is rare (Malfertheiner *et al*., 2007).

Furazolidone: it has demonstrated a high antimicrobial activity against *H. pylori* even when given as a single drug (Xiao *et al*., 1990). Primary resistance to furazolidone is nearly absent (Kwon *et al*., 2001) and its low potential to develop resistance is comparable to bismuth compounds or amoxicillin (Treiber *et al*., 2002). It achieves good eradication rates when used to replace metronidazole in both triple and quadruple therapies (Eisig *et al*., 2005) and as both second-line and third-line eradication therapies (Sotoudehmanesh *et al*., 2001). Furazolidone is a monoamine oxidase inhibitor and, as such, can interact with a number of foods and other drugs (Graham and Sung, 2006).

SEQUENTIAL THERAPY

An ideal therapy ought to be short and should lead to an eradication rate of the organism greater than 90%, as was the case initially when the triple-therapy regimens were adopted (Jafri *et al*., 2008). Recent findings however, show a decreasing efficacy of these regimens with failure rates now exceeding 20% (Liou *et al*., 2013; Vaira *et al*., 2009; Chey and Wong, 2007). This phenomenon most likely depends on an increased bacterial resistance to antibiotics, particularly against clarithromycin- the key antibiotic in *H. pylori* treatment (Vaira *et al.*, 2009).

Sequential therapy regimen consists of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and a 5-nitroimidazole (tinidazole or Metronidazole) for another 5 days (Liou *et al*., 2013; Jafri *et al.*, 2008). Several studies from Italy and other parts of the world have reported eradication rates exceeding 90% which is superior to the clarithromycin-based triple therapy (Liou *et al*., 2013; Vaira *et al*., 2009; Jafri *et al*., 2008; Chey and Wong, 2007). It is well tolerated in children, adults, and elderly patients infected with *H. pylori* (Chey and Wong, 2007). The rationale for this more complex approach is the belief that amoxicillin could weaken bacterial cell walls in the initial phase of treatment, thus preventing the development of drug efflux channels that inhibit such drugs as clarithromycin from binding to ribosomes. This may then help to improve the efficacy of clarithromycin in the second phase of treatment (Jafri *et al*., 2008). Because of this observed advantage, this therapy has a potential to become the standard first-line treatment for *H pylori* infection (Liou *et al*., 2013).

CONCLUSION

Effective diagnostic and antimicrobial therapies (multiple) are currently available for *H. pylori* management, although potent antimicrobial monotherapy has been elusive. Of note is the increasing resistance to the first line multiple antimicrobial therapies which necessitates a multistage approach to the management of the infection. Since, an ideal therapy ought to be short and should lead to an eradication rate of the organism greater than 90%, the sequential therapy seems to have a potential to become the standard first-line treatment for *H pylori* infection in the interim while search is been made for the ideal antimicrobial agent.

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