REVIEW ARTICLE

Helicobacter pylori eradication therapy: A review of current trends

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ABSTRACT

Helicobacter pylori has been implicated in the formation of chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma and gastric cancer. Eradication of *H. Pylori* has been recommended as treatment and prevention for these complications. This review is based on a search of Medline, the Cochrane Database of Systemic Reviews, and citation lists of relevant publications. Subject heading and key words used include *H. Pylori*, current treatment and emerging therapy. Only articles in English were included. There has been a substantial decline in the *H. pylori* eradication rates over the years, despite the use of proton pump inhibitor and bismuth salts for triple and quadruple therapies respectively. The reasons for eradication failure are diverse, among them, antibiotic resistance is an important factor in the treatment failure. Primary resistance to clarithromycin or metronidazole significantly affects the efficacy of eradication therapy. This has led to the introduction of second line, third line "rescue," and sequential therapies for resistant cases. Subsequently, new antibiotic combinations with proton-pump inhibitors and bismuth salts are being studied in the last decade, to find out the antibiotics that are capable of increasing the eradication rates. Some of these antibiotics include Levofloxacin, Doxycycline, Rifaximin, Rifampicin, Furazolidone based therapies. Studies are ongoing to determine the efficacy of Lactoferrin based therapy.

Key words: Bismuth salts, emerging therapies, *Helicobacter pylori*, proton-pump inhibitor

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INTRODUCTION

Helicobacter pylori, is a gram-negative, spiral bacterium situated on the epithelial surface of the stomach.[1] It is thought to be the most common bacterial infection worldwide.[2] Virtually, all persons infected by this organism develop gastritis, a signature feature of which is the capacity to persist for decades leading to chronic inflammation of the underlying mucosa.[1] It has been recognized to be associated with increased risk of chronic gastritis, peptic ulcer disease (PUD) (gastric and duodenal), gastric mucosal-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma[3] World Health Organisation (WHO) has described *H. pylori* as a class 1 carcinogen for gastric carcinoma.[3] Isolation of the organism by Warren and colleague in 1983, has modified the management of PUD.[1,3] The rate of acquisition of infection is generally higher in under-developed countries than in industrialized countries.[4] The organism can resist the harsh acidic environment of the stomach due to its high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide thereby raising the pH of the stomach and allowing it to thrive.[1]

The finding that elimination of *H. pylori* changes the natural history of PUD and MALT has led to the development of successful strategies over the years to clear the organism from persons with these disorders.

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.108884

TREATMENT OPTIONS AND INDICATIONS

In recent times, regimens that utilize proton-pump inhibitors (PPIs) in combination with several antibiotics such as clarithromycin, amoxycillin and metronidazole have been highly successful for *H. pylori* eradication.[5,6] However, recent reports detail diminishing efficacy of these combination therapies as a result of the emerging problem of antibiotic resistance both in developing and developed countries.[7]

In 1996, the European *H. Pylori* Study Group organized a meeting of specialists and experts from around the world,

representatives from National Gastroenterology Societies and general practitioners from Europe to establish updated guidelines on the management of *H. pylori* infection and was updated in the year 2000 (Maasricht 2-2000 workshop).[8,9]

TREATMENT MODALITIES

Test and treat strategy

This approach is recommended in adult patients under the age of 45 years with persistent dyspepsia, PUD, including those with complications, low-grade MALT, atrophic gastritis and following gastric cancer resection.[9]

Diagnosis of infection should be by urea breath test (UBT) or stool antigen test (SAT).[7,8]

As in the previous guidelines, successful eradication should always be confirmed by UBT or an endoscopy-based test if endoscopy is clinically indicated. SAT is the alternative if UBT is not available.

Search and treat strategy

This method of treatment is recommended for PUD patients on long-term and intermittent anti-secretory therapy, whereby patients are identified and given *H. pylori* eradication therapy. The recommended drugs include first-line therapy, which should be with triple therapy using a PPI, combined with clarithromycin and amoxicillin or metronidazole given twice daily was recommended by the European study group.[9] However, the duration of treatment varies from one geographical location to another, i.e., between 7 and 14 days. Recommended second-line therapy include bismuth based quadruple therapy with a PPI, metronidazole and tetracycline.[8,9]

SEQUENTIAL THERAPY

The decline in *H. pylori* cure rates with standard triple therapy has led to the introduction of sequential therapy. Sequential therapy in which PPI plus amoxicillin are given for 5 days followed by PPI plus clarithromycin and tinidazole also for 5 days has eradication rates close to or greater than 90%. This sequential therapy has proved to be superior than the standard triple therapy in a number of Italian studies in eradicating both susceptible and resistant *H. pylori* strains.[10] The incidence of side-effects was similar with both regimes in these trials. This treatment regimen appeared to overcome clarithromycin resistance.[10]

First-line therapy

First-line therapy is generally accepted.[9] It consists of a triple therapy using a PPI or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole for those individuals with penicillin allergy, all given twice daily, has been the corner stone of *H. pylori* eradication in many parts of the world.[8,9,11] However, even with the correct use of these drug combinations, infection is not eradicated in 10-23% of patients.[12,13] The recommended duration of treatment range between 7 and 14 days.[1,9] The emergence of drug resistance and decreasing drug efficacy, has made the second-line therapy necessary.

Second-line therapy

H. pylori may develop resistance to the prescribed antibiotics used for the first-line therapy. They may acquire resistance by acquisition and recombination of genes from other bacteria.[13] Chromosomic mutations can also induce resistance.[14] Therefore, resistance is generally thought to be the consequence of point mutations. Metronidazole targets DNA and a high mutation rate has been observed.[14] Clarithromycin and Metronidazole appear to be the two antibiotics noted for resistance and most of *H. pylori* isolates after two eradication failures are resistant to the two drugs mentioned above.[15] Subsequently, quadruple therapy which consists of PPI, bismuth, metronidazole and tetracycline is a recommended alternative to first-line treatment, which may be advocated in areas of high antibiotic resistance.[8,9,16-18] Where bismuth is not available, second-line therapy may be with PPI-based triple therapy.[8,9,11]

Third-line (rescue/salvage) therapy

This is given after multiple (at least two) treatment failures with different regimens. Ideally, it would be chosen based on the results of antimicrobial susceptibility testing.[19] Often, a careful review of agents used previously will enable a regimen to be identified that will be successful. It was noted that most of *H. pylori* isolates after two eradication failures are resistant to metronidazole and clarithromycin.[20] Therefore, it is recommended that these two drugs should be excluded from the third-line therapy.[21,22] As a result, the third-line therapy is now being applied in some countries.[23,24] These third-line therapies are the new emerging therapies.

EMERGING THERAPIES

Fluroquinolone based therapies

Levofloxacin-based triple therapies are now becoming the second-line treatment of choice in some European countries.[9] It has proven very effective in the treatment of *H. pylori* infection in a study carried out in Italy.[25] In a comparative study in Italy, the eradication rate achieved with levofloxacin-based triple therapy as a first-line treatment was significantly higher than that with standard therapies.[12] Levofloxacin has been advocated for use in second-and third-line "rescue" regimens.[26,27]

Rifabutin and rifampicin-based therapies

These are anti-tuberculous compounds. They are expensive and may not be readily available and affordable in some countries. They are associated with some side effects like myelotoxicity, leucopaenia and thrombocytopaenia.[28,29]

This therapy has been found to be effective in combination with a PPI and amoxicilin.[13,20,29,30] However, the main problem with a widespread use of rifabutin and rifampicin is the concern that antibiotic resistance may develop against *Mycobacterium avium* in HIV-infected patients. It has been suggested to reserve the use of rifabutin for the treatment of multi-drug resistant *Mycobacterium tuberculosis* strains.[31] Therefore, the use of this drug for *H. pylori* eradication is being discouraged.[13]

Furazolidone-based therapy

Furazolidone is active against gram-negative, gram-positive bacteria (including *H. Pylori)* and protozoa by inhibiting bacterial enzymes.[32] It is widely used in low-income populations because it is inexpensive.[13] Strains resistant to furazolidone are rare and its potential to develop resistance is as low as bismuth compounds or amoxicillin.[33]

One-week quadruple regimen with lansoprazole, bismuth, tetracycline and furazolidone, has shown an eradication rate of 90% as third-line therapy in 10 patients with metronidazole resistance by culture.[34]

Doxycycline-based therapy

Doxycycline is a widely used tetracycline antibiotic for several infections. With respect to tetracycline, doxycycline requires the administration of only two capsules per day, leading to a better compliance in patients undergoing eradication therapies.[13] Furthermore, a study has found no secondary resistance to doxycycline in *H. pylori* isolates from patients who failed one or more eradication therapies.[35] Quadruple regimens represent the most widely used rescue therapy.[13] In cases of metronidazole resistance, a new practice, namely replacing tetracycline with doxycycline, one-week quadruple therapy with doxycycline, amoxicillin, omeprazole and bismuth salts. This treatment has proved to be a highly effective third-line 'rescue' therapy, achieving 91% eradication rate in patients harboring metronidazole and clarithromycin resistant *H. pylori* strains (by ITT analysis). This regimen, showing excellent compliance (99%) and mild side-effects, may well constitute the best available option for the third-line rescue treatment.[15]

Lactoferrin

Lactoferrin is a natural antibiotic found in bovine milk. It has been found to be bacteriostatic to *H. pylori* both *in vivo* and *in vitro*.[36] It is a milk protein that binds iron, and its addition to the regular treatment regimen for *H. pylori* may improve eradication rates.[37] Studies have been carried out to determine its use in combination with PPI and other antibiotics with varying efficacies.[38] This modality of treatment has not been universally accepted.

Levofloxacin and rifaximin-based quadruple therapy

Levofloxacin and rifaximin-based quadruple regimen as first-line treatment for *H. pylori* infection has been studied by Choi *et al*.,[39] but has limited efficacy in a Korean cohort. Further multi-centred studies may be required in other countries.

CONCLUSION

Despite the introduction of the first, second and third line therapies for *H. pylori* eradication, the eradication rate has not reached 100%. Antibiotic resistance is still a problem in many countries. To face treatment failures, several third-line 'rescue' therapies have been tried. This third-line therapy has not been used in many countries. Our review shows that further trials are still needed to get a better *H. pylori* eradication rate.

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How to cite this article: Olokoba AB, Obateru OA, Bojuwoye MO. *Helicobacter pylori* eradication therapy: A review of current trends. Niger Med J 2013;54:1-4.

Source of Support: Nil, **Conflict of Interest:** None declared.