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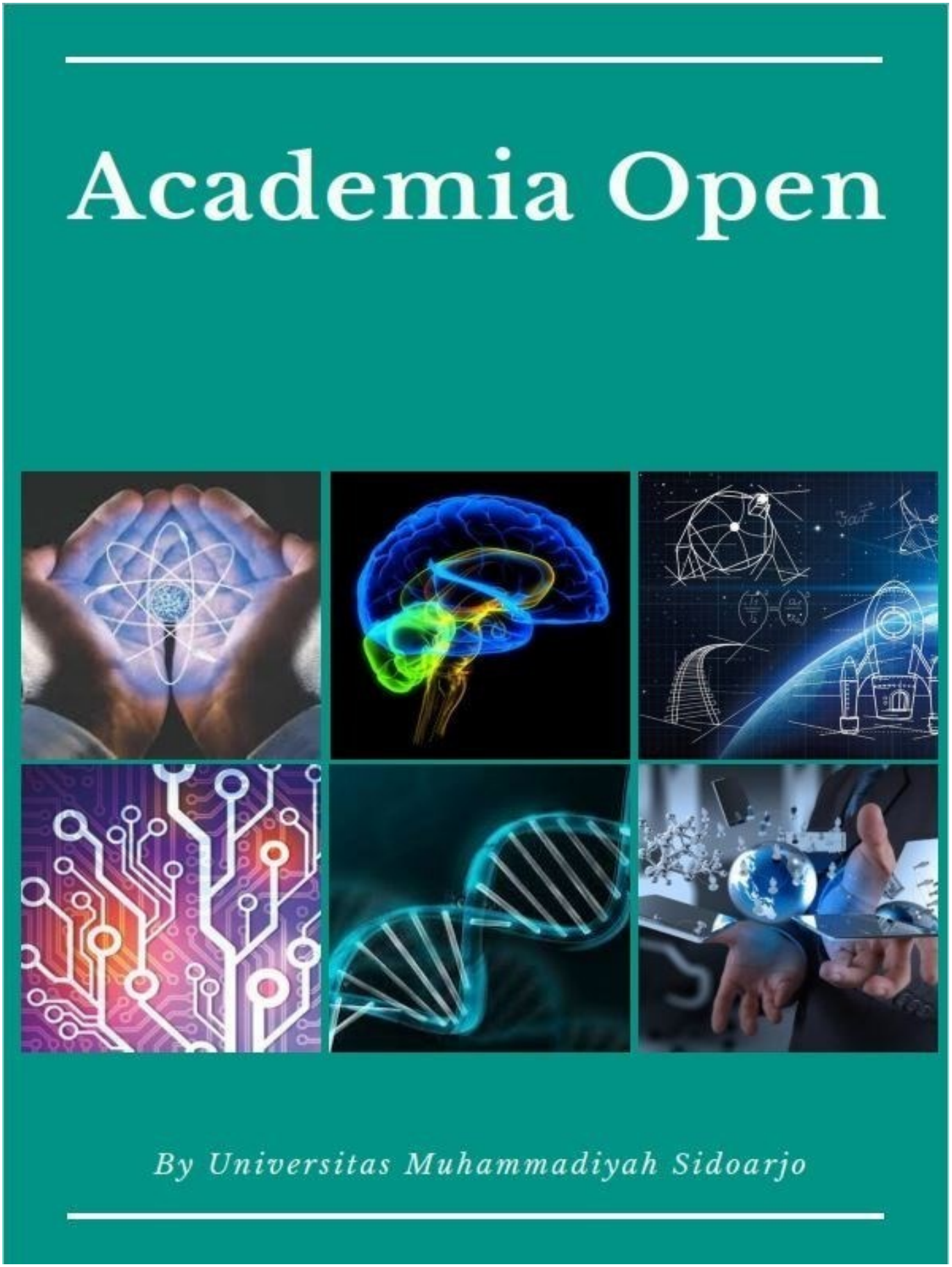

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Helicobacter pylori Infection: From Pathogenesis to Clinical Management

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Abstract

General Background: Helicobacter pylori represents a gram-negative bacterium colonizing gastric mucosa in approximately half of the global population, recognized as the primary causative agent of chronic gastritis, peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. **Specific Background:** The bacterium employs sophisticated virulence factors including cytotoxin-associated gene A and vacuolating cytotoxin A to establish chronic infection, triggering persistent inflammatory responses that progress through atrophic gastritis, intestinal metaplasia, and dysplasia toward malignancy. **Knowledge Gap:** Despite advances in understanding pathogenesis and treatment protocols, escalating antibiotic resistance threatens conventional eradication strategies, necessitating comprehensive evaluation of current diagnostic approaches and therapeutic interventions. **Aims:** This review systematically examines the microbiology, pathogenesis, epidemiology, clinical manifestations, diagnostic methods, and treatment strategies for H. pylori infection, with particular emphasis on antibiotic resistance patterns. **Results:** Evidence demonstrates that bismuth-based quadruple therapy achieves 80-90% eradication rates even in clarithromycin-resistant regions, while H. pylori eradication significantly reduces gastric cancer risk when implemented before precancerous lesion development. **Novelty:** The analysis integrates molecular resistance mechanisms with population-based epidemiological patterns to inform personalized treatment selection. **Implications:** Sustained multidisciplinary collaboration remains essential for developing novel antibiotics, rapid susceptibility testing, and effective vaccines to reduce global H. pylori disease burden.

Keywords : Helicobacter Pylori, Gastric Cancer, Peptic Ulcer Disease, Antibiotic Resistance, Diagnostic Methods

Highlight :

- Bacterium infects approximately 4.4 billion individuals worldwide with varying regional prevalence rates.
- Clarithromycin resistance reaches 50% in some regions, reducing triple therapy effectiveness significantly.
- Early eradication prevents gastric cancer progression when administered before precancerous lesion onset.

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Introduction

Helicobacter pylori is a microaerophilic gram -negative bacterium, which has coevolved with humans at least 60,000 years and inhabits the gastric mucosa of about 4.4 billion individuals worldwide (1). The spread of H. pylori infection among various geographical areas and populations is also highly uneven with higher prevalence among 3 rd world and underprivileged countries where the infection is usually acquired in childhood and continues throughout life unless it is treated (2). The fact that the bacterium is capable of surviving in the extreme acidic conditions of the stomach is also a great adaptation that has caused it to become one of the most successful human pathogens.

H. pylori infection has far more than a high prevalence clinical significance. The bacterium has a causal relationship with chronic active gastritis in practically all infected individuals albeit most of them remain asymptomatic carriers in their lifetime (3). Nevertheless, about 10-15 per cent of infected people get peptic ulcer disease and 1-3 per cent of them get gastric cancer hence H. pylori is the best-recognized risk element in gastric adenocarcinoma (4). In 1994, the International Agency on Research in Cancer (IARC) categorized H. pylori as a Group I carcinogen, which has an unquestionable carcinogenic potential in humans (5).

The fact that H. pylori was found has fundamentally altered our knowledge on gastroduodenal pathology. Before the discovery of this bacterium, peptic ulcer disease was mainly caused by the overproduction of acid and stress and treatment was based on acid suppression and lifestyle changes. The identification of the fact that the majority of peptic ulcers are due to a bacterial infection that is controlled through antibiotics was a paradigm shift in the field of gastroenterology (6). In spite of such developments, there are still concerns that are related to the treatment of H. pylori infection specifically increased incidences of antibiotic resistance and the necessity of better diagnostic techniques and treatment plan.

Microbiology and Pathogenesis.

A. Bacterial Characteristics

H. pylori is a gram negative, spiral shaped bacterium that has a length of about 2.5-5.0 micrometers and width of 0.5-1.0 micrometers (7). The bacterium has 4-6 single-polar flagella, which confer it motility, which is necessary to penetrate the gastric mucus layer and colonize it. The flagella are covered and it has flagellin subunits which play the role of providing movement and chemotaxis to the gastric epithelium (8). Important virulence factors include the spiral morphology and motility of the bacterium that allow the passage of the bacteria through the thick layer of the mucus.

The bacterium uses a number of enzymes to help it to survive in the gastric environment. The most common protein secreted by H. pylori is Urease, which catalyzes the breakdown of urea into ammonia and carbon dioxide to form an alkaline environment that helps the bacterium to avoid gastric acid (9). This enzyme is important to the survival of H. pylori to the extent that it is both a diagnostic marker and a target of therapy. The other enzymes that are significant are catalase and superoxide dismutase, which safeguard the bacterium against oxidative stress, and mucinase, which disprese the protective mucus layer (10).

B. Virulence Factors

H. pylori has a number of virulence factors that are related to its pathogenicity, and its disease outcome. Cytotoxin-associated gene A (CagA) protein is among the most significant virulence determinants. The type IV secretion system that delivers CagA into gastric epithelial cells is coded by the cag pathogenicity island (cag PAI) (11). After getting into the cell, CagA is phosphorylated on tyrosine and is associated with various intracellular signaling pathways which result in dysfunction of the cells, inflammation in the cells, and predisposition to gastric cancer (12).

Another virulence factor that is essential and causes vacuoles to form in epithelial cells, disrupting tight junctions and promoting apoptosis is the vacuolating cytotoxin A (VacA) (13). The vacA has several allelic forms that vary in their cytotoxic capability and some of them are related to higher levels of severe disease outcomes. Other key virulence factors are blood group antigen-binding adhesin (BabA), which facilitates bacterial adherence to gastric epithelial cells, and the gene that promotes duodenal ulceration (DupA) that is linked to a high risk of duodenal ulceration (14).

C. Host-Pathogen Interactions

H. pylori and the host immune system closely interact, which defines the clinical outcome of infection. When H. pylori is colonized, it results in the induction of innate and adaptive immune responses and the subsequent inflammatory condition of the gastric mucosa (15). The bacterium triggers the pattern recognition receptors such as Toll-like receptors (TLRs) especially TLR2, TLR4 and TLR5, which stimulate the inflammatory signaling cascades and the production of cytokines (16). The upregulation of pro-inflammatory cytokines such as interleukin-1b (IL-1b), IL-6, IL-8, tumor necrosis factor-alpha (TNF-a) is observed in the case of H. pylori infection.

In spite of strong immune reactions, the host does not clear the infection of H. pylori, which results in chronic colonization and continuous inflammation. A number of bacterial mechanisms are involved in evading the immune response such as LPS-modifications that decrease the TLR4-activation, the expression of arginase which empties arginine required to activate T-cells, and the induction of regulatory T-cells to inhibit an effective immune response (17). The inflammatory disease caused by the enduring H. pylori infection predisposes gastric mucosa with changes such as atrophy, intestinal metaplasia, dysplasia, which are sequential stages of the cascade of pathogenesis of gastric cancer (18).

D. Genetic Diversity

H. pylori has an incredible genetic diversity and virtually there is none that is genetically identical to another. This is due to the large rate of mutation, frequent recombination and horizontal gene transfer (19). Genetic heterogeneity of H. pylori has significant clinical consequences due to the fact that the strains differ in their ability to be virulent, and in terms of the diseases they are associated with. The population genetic analysis has revealed the presence of specific H. pylori populations related to the pattern of human migration, as the ancient coevolution of this bacterium with human hosts (20).

Viral genes are disseminated differently across various populations of H. pylori. The strains that contain cagA are predominant in some geographical areas and are linked to the high risk of peptic ulcers and gastric cancer (21). On the same note, highly cytotoxic VacA variants are more common among different groups of people. This genetic diversity is significant in the future, as it helps to predict the possibility of a disease,

create specific medications, and create effective vaccines (22).

Epidemiology and Transmission.

A. Global Prevalence

The H. pylori infection rate is estimated as about 50 percent all over the world, with significant variations across nations and among nations (23). Higher rates are normally as seen in developing countries, which tend to be above 70-80 percent in some areas, whereas low rates are found in developed countries which are usually between 20-40 percent (24). This gap is associated with socioeconomic status, sanitation system, population, and healthcare access. It is worth mentioning that the prevalence rates in the developed world have been steadily decreasing over the past decades due to better living conditions, the high usage of antibiotics to treat various diseases, and some changes in the eating habits (25).

There are differences in the age specific pattern of prevalence between high and low prevalent regions. Childhood acquisition is the most common in developing countries whereby by the time they reach adolescence, prevalence rates have reached the adult rates (26). Conversely, the cohort effect is demonstrated in developed nations where the prevalence is higher in older age groups due to the acquisition of infection in the previous decades when the living conditions were not as good. These patterns of epidemiological interest have significant disease burden and prevention implications (27).

B. Transmission Routes

The transmission mechanisms of H. pylori have not been fully understood but the transmission between individuals is believed to be the most important. There is evidence of both fecal-oral and oral-oral routes (28). Feces, saliva and dental plaque can harbor the bacteria and this supports the transmission routes. The transmission within a certain family is frequent, and the research has shown that there exists clustering of infection and same strain of organism within a family (29). It seems that mother-to-child transmission in early childhood is of especial significance and this may be by oral-oral contact or through exposure to contaminated maternal saliva.

It can also be transmitted through environmental factors especially in areas where the water treatment and sanitation is poor. H. pylori is also known to be present in water sources but whether water is a major mode of transmission is still debatable (30). The socioeconomic factors greatly determine the transmission risk, and crowded living conditions, the sharing of eating utensils and beds, and the absence of running water are all related to the increase in the rate of infections. The transmission dynamics is an essential factor in the formulation of effective prevention measures, whereas the vaccine has not been discovered yet despite the continuous research efforts (31).

Clinical Manifestations

A. Chronic Gastritis

The proactive gastritis is observed in practically everyone who is infected with H. pylori, being the underlying disease presentation (32). Inflammatory process usually starts in the gastric antrum and has the potential to extend to the corpus which subsequently results to pangastritis. H. pylori gastritis histologically is characterized by neutrophil, lymphocyte, plasma cell, and macrophage infiltration of the lamina propria. Bacterial factors, host genetics and environmental factors play a role in the intensity and distribution of the inflammatory response (33).

Most of the infected people are asymptomatic even though there is still inflammation but a few develop dyspeptic symptoms. H. pylori gastritis has predictable patterns of natural history, with inflammation possibly having sequential phases of atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately gastric adenocarcinoma in a proportion of patients. The process is referred to as the Correa cascade and refers to the process taking place over decades and is affected by several cofactors such as strain virulence, host genetics, dietary factors and environmental exposures (34).

B. Peptic Ulcer Disease

H. pylori infection is found in about 70-90% of duodenal ulcers and 60-70% of gastric ulcers and is the cause of peptic ulcer disease of the world (35). These processes that attribute H. pylori to the development of ulcers are multifactorial and comprise of elevated gastric acid discharge, decreased antral somatostatin-producing D cells, defective duodenal acid discharge, and direct mucosal harm caused by inflammatory cytokines and bacterial toxins (36). The development of duodenal ulcers is usually associated with antrum-predominant gastritis, which maintains or increases acid secretion whereas gastric ulcers are usually corpus-predominant gastritis with decreased acid secretion.

The clinical conditions of peptic ulcer disease differed and the conditions are characterized by the presence of pain in the epigastric area that can be alleviated either by taking food or taking antacids (37). The complications are bleeding, perforation, and gastric outlet obstruction. Notably, H. pylori eradication radically decreases the rates of ulcer recurrence, which is about 60-70 years on average and reduces them to not more than 10 years, completely altering the natural history of peptic ulcer disease (38). The existing recommendations suggest that H. pylori should be tested and eliminated in every patient with peptic ulcer disease.

C. Gastric Cancer

Gastric adenocarcinoma is the most serious complication of the infection caused by H. pylori which is the third most dangerous cancer-related death among the global population (39). The epidemiological research indicates that, H. pylori-infected persons are more likely to develop gastric cancer by 2-6 folds than uninfected persons with the risk of gastric cancer being significantly higher in case of CagA-positive strains infection (40). Pathogenesis This is a multistep chronic inflammation process resulting in gastric atrophy, intestinal metaplasia, dysplasia, and finally invasive carcinoma.

Host genetic factors, bacterial virulence determinants, and environmental cofactors such as high salt intake, smoking, etc., can moderate the risk of getting gastric cancer in H. pylori-infected people, although not every one of them develops the cancer (41). Gene polymorphisms of inflammatory mediators, especially IL-1b and TNF-a, are factors that determine the cancer susceptibility. Removal of H. pylori decreases the prevalence of gastric cancer especially when it has been conducted before the onset of precancerous lesions, and this is a reason to support the idea of population-based screening and treatment interventions in areas at risk (42).

D. MALT Lymphoma

MALT lymphoma is a well-known but uncommon effect of H. pylori infection in gastric mucosa. Clonal B-cell proliferation occurs due to the chronic antigenic stimulation that results in the development of lymphoma through persistent bacterial infection (43). MALT lymphoma is a disease that occupies about 5 percent of gastric cancers and has a strong correlation with H. pylori where infection has been reported among more than 90 percent. The lymphoma is usually localized in the gastric mucosa and submucosa as a localized disease.

Surprisingly, the treatment of early-stage MALT lymphoma has been effectively carried out by eradication of H. pylori alone with complete remission in some 60-80% of the cases (44). It is a rare case of malignancy treatment with the use of antibiotics. Nevertheless, tumors with some genetic abnormalities, especially t(11;18) translocation are not as susceptible to eradiation therapy and may need other therapy measures such as chemotherapy or radiotherapy (45). H. pylori should also be tested on all patients with MALT lymphoma with eradication therapy being given to those who test positive.

Diagnostic Methods

A. Invasive Tests

Diagnostic techniques implemented are invasive procedures that involve endoscopy, including biopsy of the stomach. Rapid urease test (RUT) is relatively common as it is simple, inexpensive and quick (46). Biopsies are immersed in a liquid or gel media with urea and a pH indicator; urease generated by H. pylori breaks urea and increases pH and a color change occurs. Results will be given in a matter of minutes to hours but given the recent use of proton pump inhibitor (PPI), antibiotics or bismuth compounds sensitivity may be compromised. Several biopsies of antrum and corpus enhance precision in diagnosis.

The H. pylori diagnosis is still the gold standard of histological examination to enable direct visualization of the bacteria and evaluation of related gastric pathology that includes inflammation, gastric atrophy, and intestinal metaplasia (47). H. pylori is detected by Hematoxylin and eosin but special stains such as Giemsa, silver staining in the Warthin-Starry or immunohistochemistry react to increase sensitivity. Gastric biopsies culture can be used to isolate bacteria, test antibiotic sensitivity, and characterize strains but it is demanding in technology, time consuming and requires special expertise (48). Culture is also useful especially where there is failure to treat by providing guidance on antibiotic choice.

B. Non-Invasive Tests

UBT is a very precise test, the sensitivity and specificity rate is more than 95% in research (49). The patients take urea containing carbon-13 or carbon-14; urease in H. pylori degrades the labelled urea releasing carbon dioxide labelled with carbon-13 or carbon-14 which is absorbed through the blood and breathed out. The test is not invasive, is well-tolerated, and is especially applicable to verify eradication following treatment. Nevertheless, PPIs, antibiotics, and bismuth should be stopped with due intervals before the tests in order to prevent false-negative outcomes.

Stool antigen tests are tests that are used to detect the H. pylori antigens in the feces through enzyme immunoassay or immunochromatographic methods (50). Monoclonal antibody tests prove to be accurate and can be used both in initial diagnosis and in eradication confirmation. Antibodies to H. pylori are detected serologically, usually by ELISA. Even though it is convenient and cheap, serology does not work well due to the fact that the antibodies linger on months to years even when the treatment is completely successfully eradicated hence not suitable in establishing treatment success (51). Serology can be applicable in certain conditions such as those who are actively bleeding and those under PPIs when other tests can give false-negative results.

Treatment Strategies

A. First-Line Therapies

The most commonly used first-line regimen was standard triple therapy, which comprised of a PPI, clarithromycin, and amoxicillin or metronidazole in 14 days (52). Nevertheless, the growing resistance to clarithromycin has affected the efficacy in numerous areas, and the current guidelines indicate that triple therapy needs to be employed in areas where the clarithromycin resistance is reported to be less than 15% (53). With its use, the course of treatment of 14 days is better than that of 7-10 days, with higher eradication rates.

The use of bismuth-based quadruple therapy as a combination of a PPI, bismuth, tetracycline, and metronidazole has become a desirable first-line choice in most centers because of its effectiveness even in areas with high clarithromycin resistance (54). This treatment gives a result of 80-90% eradication in the majority of the studies. An alternative effective single-line therapy is concomitant therapy with a PPI, clarithromycin, amoxicillin and metronidazole at the same time, during 10-14 days, which is especially effective in areas where clarithromycin and metronidazole have dual resistance (55). Sequential therapy, which includes a PPI and amoxicillin during the initial 5-7 days and a PPI, clarithromycin, and metronidazole during the second 5-7 days has produced varied outcomes in the various groups.

B. Antibiotic Resistance

The greatest impediment in successful eradication of H. pylori is antibiotic resistance. The levels of primary resistance to clarithromycin have also become worrying all over the world, with many countries reporting above 15 percent of resistance and others with nearly 50 percent resistance rates (56). Resistance to Clarithromycin is mainly caused by point mutations in the 23S rRNA gene that inhibit attachment of antibiotics with the ribosome. Metronidazole resistance is also prevalent especially in developing nations although its clinical effects are less dependable because this resistance can at times be eluded by increasing doses or increasing treatment period (57).

Amoxicillin and tetracycline resistance is rare in most parts of the world, and hence these antibiotics are valid ingredients of eradication programs (58). Geographical patterns of resistance are however not universal and local resistance data should preferably be used to inform making of treatment choices. Molecular techniques to detect resistance-related mutations in the gastric biopsies/stool sample require further development and could be used in the future to allow individual selection of therapy. The WHO has put the H. pylori which has clarithromycin resistance in its list of priority antibiotic-resistant bacteria that urgently require new treatment (59).

C. Rescue Therapies

Rescue treatment choice is determined by the first-regimen and the local resistance patterns when there is failure of first-line therapy. An effective

rescue therapy that may be used to rescue a situation involving triple therapy failure is bismuth-based quadruple therapy (60). Triple therapy (PPI, levofloxacin, amoxicillin) based on levofloxacin has been employed both as a rescue treatment, but the emergence of resistance to fluoroquinolone in most areas has limited its usefulness (61). The third-line or rescue treatment is based on Rifabutin, but is restricted due to its high cost, the occurrence of some side effects, and its potential to encourage resistance to a major anti-tuberculosis medication.

To select an antibiotic, culture and antimicrobial susceptibility testing ought to be taken into consideration following several treatment failures (62). Dual therapy of PPI and amoxicillin at high dosage has been demonstrated to be successful in certain studies, especially where PPIs are administered more than once per day. New strategies in research are optimization of PPI dosing by pharmacogenetic testing of CYP2C19 polymorphism, which affect the metabolism of PPI, and inclusion of probiotics to regular doses, although the benefits of probiotics are not always evident (63).

Conclusion

Helicobacter pylori infection is a significant health issue in the world with an estimated prevalence of half a billion people, with a considerable morbidity rate in the form of peptic ulcer disease, gastric cancer, and MALT lymphoma. This has made the bacterium an object of intense study in more than 40 years due to both exceptional adaptation to the gastrointestinal environment and the highly intricate interplay between the bacterium and the immune system of the host organism. H. pylori discovery was the new step in the history of gastroduodenal pathology as it proved that bacterial infections might be the cause of chronic illnesses and cancer and shattered the medical paradigms.

Much has been achieved to comprehend the pathogenesis of H. pylori, diagnostic techniques, and effective therapies. Nevertheless, the challenges are still significant, the most prominent among them being the increase of the incidence of antibiotic resistance that endangers the effectiveness of conventional eradication protocols. Innovative treatment methods, i.e. new antibiotics, better drug delivery technologies, and possibly vaccines are essential in the process of keeping the capability of effective treatment of this infection. The need to understand patterns of local resistance and adjust treatment plans to suit them and creating rapid tests of susceptibility will be critical in ensuring high treatment outcomes.

The future research trends entail understanding the mechanisms of resistance to antibiotics and devising ways to overcome it, enhancing diagnostics of resistance detection, elucidating factors that lead to clinical outcomes in those infected, as well as the development of effective vaccines. Screening and treatment of high-risk areas by using population-based methods can minimize the burden of gastric cancer, but these initiatives must consider the cost-effective methods, implications of antibiotic resistance, and the health infrastructure within the countries. It will be necessary to sustain cooperation between microbiologists, gastroenterologists, epidemiologists, and the specialists of health care in order to overcome the current dilemma of the H. pylori infection and decrease the number of people affected globally.

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