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"HELICOBACTER PYLORI MANAGEMENT GUIDELINES FROM PAKISTAN"

On Behalf of Pak GI and Liver Disease Society (PGLDS) & Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP)

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Primary Objective

To devise a local guideline from Pakistan for physicians, giving a holistic overview of the current evidence of disease demographics, management, challenges, and recommendations of Helicobacter Pylori in line with international standards.

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MESSAGE

PROF. LUBNA KAMANI

PRESIDENT PAK GI & LIVER DISEASE SOCIETY

Helicobacter Pylori (HP) infection is one of the commonest infection leading to peptic ulcer disease and gastric cancer in Pakistan and worldwide. Patients often present with common chronic upper gastrointestinal symptoms and delayed diagnosis can lead to gastric cancer in some cases. Prompt identification with appropriate testing and managment with judicious use of antibiotics is the key for successful eradication of this infection.

Currently, there is no standard Helicobacter guidelines in Pakistan. Keeping this in mind Pak GI and Liver disease society (PGLDS) and Medical Microbiology and Infectious Disease Society of Pakistan (MMIDSP) joined hands for Publication of first comprehensive Helicobacter Guideline from Pakistan. These guidelines are compiled keeping in mind of the local demographics, availability of HP tests and presence of antimicrobial resistance pattern in Pakistani community at large.

This is a collaborative effort with holistic approach by a group of national experts. It can be utilized as a reference document by General Practitioners, internists, family physicians, gastroenterologists and medical students. I am confident that these guidelines will help and support health care professionals for better patient management, which will lead to improved outcomes.

Lastly, I would like to express my utmost gratitude to Getz Pharma and its entire team for efficient and structured administrative support from the beginning to the end.

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MESSAGE

PROF. BUSHRA JAMIL

PRESIDENT, MEDICAL MICROBIOLOGY & INFECIOUS DISEASE SOCIETY OF PAKISTAN

Helicobacter pylori infection and disease are rampant in Pakistan. Because of our unique environmental challenges and unregulated use of antibiotics, treatment and eradication of many infectious agents has become problematic. Local context and susceptibility data are the two most important aspects of management of any disease, and more so for H pylori because of its high prevalence.

I would like to congratulate Prof. Lubna Kamani and her team for successfully developing this very important and long-awaited document, on behalf of Pak GI and Liver Disease Society (PGLDS) and Medical Microbiology and Infectious Disease Society of Pakistan (MMIDSP). The group work and dedication of team members from initiation to completion of the national guideline is a landmark achievement. I would also like to thank Getz Pharma for their technical and logistic support for this timely initiative. This document will go a long way in guiding appropriate management of H. pylori infections disease in Pakistan.

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GUIDELINES

Helicobacter Pylori Management Guidelines from Pakistan

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"On Behalf of Pak GI and Liver Disease Society (PGLDS) & Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP)"

Primary Objective

To devise a local guideline from Pakistan for physicians, giving a holistic overview of the current evidence of disease demographics, management, challenges, and recommendations of Helicobacter pylori in line with international standards.

Introduction

Helicobacter pylori (H. pylori) is a Gram negative bacteria that resides in various parts of stomach, particularly the antrum. It was first discovered in 1982 and is thought to play a role in the root cause of a variety of Gastrointestinal (GI) diseases that include chronic active gastritis with or without clinical complaints, peptic ulcer (PU) and gastric adenocarcinoma. Chronic H. pylori infection induces atrophic and even metaplastic alterations in the stomach, as well as a link to peptic ulcer disease. In less developed Asian nations such as India, Bangladesh, Pakistan, and Thailand, the prevalence of H. pylori infection is significant. The global prevalence of H. pylori infections varies between 10% and 90%.[1]

Helicobacter pylori is still a considerable health issue around the world. Infection with H. pylori almost always results in active chronic gastritis. Most people are clinically asymptomatic for the rest of their lives, but a significant percentage develop gastroduodenal disorders, including PU disease, non-cardia stomach cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[2]

Clinicians are still searching for the most effective, safe, and easy management, The problem of antimicrobial resistance to therapy is a major challenge.

According to the Global Burden of Disease, India has the largest prevalence of PU disease, with 2 million people afflicted, while the Nordic region has the lowest prevalence, with only roughly 22000 people.[3] In a local study, prevelance of H. pylori was as high as 92%.[4]

Faeco-oral, oral-oral and contaminated water and food supplies serve as important and key factors of H. pylori transmission among the developing world including Pakistan.

A large survey on Pakistani population revealed lower scioecnomic status, low level of education and increasing age was associated with seropositivity among participants.[5]

From one of the published meta-reviews, it was observed that Africa had one of the highest prevalence (70.1 %); while Oceania had the lowest incidence (24.4%). The prevalence of H pylori infection varied greatly between countries, ranging from 18.9% in Switzerland to 87.7% in Nigeria.[6]

The disability-adjusted life years (DALYs) for peptic ulcer disease in Pakistan is 0.1 milliion which is significantly lower than neighbouring countries like India & China (Figure-1).[3]

The prevalence of PUD in India tops the list with 2 million individuals whereas Pakistan is the third least prevalent country with the total count of 0.21 million (Figure-2).

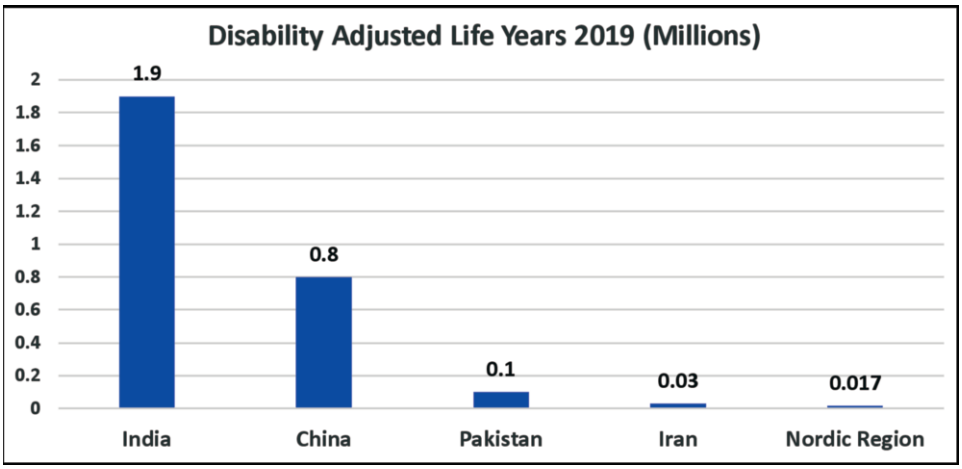

Figure-1: Peptic Ulcer Demographics in Asia & Nordic Region; Disability Adjusted Life-years (2019 data) Adapted from the data obtained from the global burden of diseases.[3]

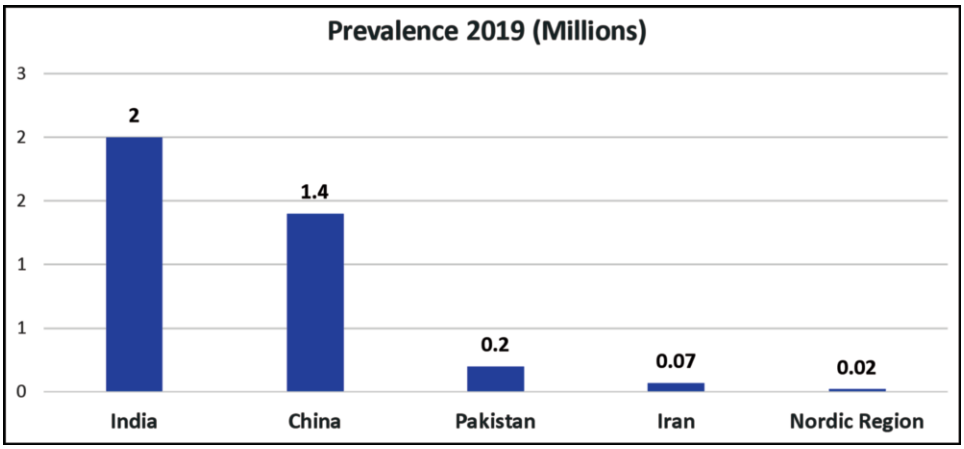

Figure-2: Prevalence of Peptic Ulcer in Asia & Nordic Region; (2019 data) Adapted from the data obtained from the global burden of diseases.

Indications for Helicobacter Pylori Testing[7]

Table-1: Absolute and relative indications for H. Pylori testing.

Absolute	Relative
Peptic Ulcer Disease	Uninvestigated dyspepsia & younger than 60years (non-endoscopic testing)
History Of PUD	Low-dose aspirin usage over a long time
Low-grade gastric mucosa-associated Lymphoid tissue (MALT) Lymphoma	Patients who require long acting PPI for GERD
Dyspepsia undergoing upper endoscopy	Patients who are immediate relatives of stomach cancer patients
Initiating chronic NSAID use	IdiopathicThrombocytopenic Purpura
Despite thorough assessment, unexplained iron deficiency anaemia	
ITP&past history of endoscopic resection of early gastric cancer	

Insufficient Evidence for H. Pylori Testing[8]

- No history of PUD and typical GERD symptoms
- Asymptomatic with a family history of stomach cancer
- Lymphocytic Gastritis
- Acne Rosacea and Chronic Urticaria
- Hyperplastic Gastric Polyps
- Hyperemesis Gravidarum

Table-2: Available diagnostic methods for H. pylori.

Pre-treatment Tests

Diagnostic Test	Procedure	Pros	Cons
Blood Test (H. Pylori Serology/ Antibody)	A blood sample is used for the test. Blood is drawn from a vein in arm or hand using a needle.	• No preparation is needed • Readily available • Cost-effective	• The downside is that the test stays positive for an extensive period despite a previous H. Pylori infection been treated • Not recommended in Pakistan due to high prevalence[9]
Urea Breath Test (UBT)	A tablet containing urea is given to the patient (C_{13} or C_{14}). H. Pylori can be detected after 20 to 30 minutes by blowing a sample of patient's breath into a little balloon-like bag.	• Simple, Non-invasive, cost-effective, safe • Not widely available in Pakistan especially in remote and small district hospitals • There are two types of UBT, radioactive and non-radioactive • The radioactive isotope is not recommended in pregnant women • Best to avoid UBT in pregnancy unless testing outweighs the risk	• False- +ve test findings in achlorhydria, as well as oral microorganisms with urease activity. • Patients having a history of stomach surgery have lower reactiveness. • Another urease-producing bacteria, Helicobacter heilmannii, can produce false-+ve tests. • PPI therapy must be stopped at least 10-14 days before the procedure.
Stool Test (H. Pylori Antigen)	The stool is analyzed for H. Pylori antigens	• Non-invasive, cost-effective, safe in children and pregnant women • It can confirm that the infection has been cleared after treatment	• Antibiotics & antacids can interfere with the accuracy of the test • PPI treatment needs to be stopped at least 10-14 days prior • Stool sample collection is cumbersome
Endoscopy	After conscious sedation, a long flexible tube with a tiny camera at the front is pushed down the neck and esophagus, and into the stomach, where a biopsy for H. Pylori is obtained.	• It's a quick procedure • Usually isn't painful • Rapid urease test can be done with biopsy and results are available within 30 minutes • A biopsy can also be sent for histopathology (gold-standard)	• Invasive & can cause discomfort • The patient is sedated pre-procedure • Histopathology reporting can take around a few days

Treatment Options

First-line Regimens

Table-3: First-line regimens:*Dose; orally administered PPIs include: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, or esomeprazole 20 mg daily)

Regimen	Drug & Doses	Duration
Clarithromycin Triple	Proton Pump Inhibitor (standard*OR2 x standard dose) 500 mg Clarithromycin BID 1 gm Amoxicillin BID OR 500 mg Metronidazole TID	10-14 days
Quadruple Including Bismuth	PPI (Dose*) 120 to 300 mg Bismuth sub citrate QID OR 300 mg Bismuth Subsalicylate QID 500 mg Tetracycline QID 250 mg Metronidazole QID OR 500 mg TID or QID	10-14 days
Sequential	Proton Pump Inhibitor(standard* or 2 x standard dose) plus amoxicillin 1 g BID Proton Pump Inhibitor (standard dose*) plus 500 mg clarithromycin BID plus 500 mg nitroimidazole twice daily	5 days each
Levofloxacin Sequential	Proton Pump Inhibitor (standard* or double the standard dose) plus amoxicillin 1 g BID Proton Pump Inhibitor (standard* or double the standard dose) plus 1 gm amoxicillin BID plus 500 mg nitroimidazole BID plus 500 mg levofloxacin OD	5-7 days

Salvage Therapies

If first-line treatment fails, retreat using salvage therapy. Moreover, avoid regimens that contain previously-used antibiotics.

Table-4: Salvage therapies (Standard doses of orally administered PPIs include: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, or esomeprazole 20 mg daily).

Regimen	Drug & Doses	Duration
Quadruple Including Bismuth	PPI (standard dose*) 120 to 300 mg Bismuth sub citrate QID OR 300 mg bismuth subsalicylate QID Tetracycline 500 mg QID Metronidazole 500 mg TID or QID	14 days
Triple Including Levofloxacin	Proton Pump Inhibitor (standard dose*) 1g Amoxicillin BID 500 mg Levofloxacin OD or 250 mg BID	14 days

Second-line Regimens

Table-5: Second line regimens.

Regimen failures	Maastricht V/Florence Consensus Report, 2016[10]	Toronto Consensus Report,2016 [11]	WGO Guidelines
If clarithromycin-triple therapy fails in the first-line setting,	• Quadruple Bismuth*[1] • Levofloxacin-triple or quad	• Bismuth quad • Levofloxacin triple	• Quadruple
Upon failure of bismuth quad in the first round.	• Levofloxacin-triple or quadruple • In cases of high Levofloxacin resistance: 1. Bismuthwith other antibiotics 2. Rifabutin triple	• Levofloxacin triple**[2]	• Clarithromycin or levofloxacin triple therapy
Upon failure of non-bismuth quad as first-line	• Bismuth quad • Levofloxacin triple orquad	• Levofloxacin triple	• levofloxacin-based therapy
For More than two (2) treatment failures	• Treatment guided by results of resistance testing	• Avoid reusing clarithromycin, levofloxacin, Metronidazole. • Consider rifabutin tripleafter >3 failures	• High Dose Dual Therapy

*Quadruple Bismuth: PPI (standard dose) twice daily for 10 to 14 days, 120 to 300 mg Bismuth sub citrate 4 times per day OR 300 mg Bismuth subsalicylate 4 times per day, 500 mg Tetracycline 4 times per day, 250 mg Metronidazole 4 times per day OR 500 mg 3 or 4 times per day.[1]
**Levofloxacin Triple: PPI (standard dose) twice daily, 1 gm Amoxicillin twice daily, 500 mg Levofloxacin once daily or 250 mg twice daily for 14 days.[2]
Note: Standard doses of orally administered PPIs include: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, or esomeprazole 20 mg daily.

Treatment in People with Penicillin Allergy

In penicillin allergy patients, true penicillin hypersensitivity is rare. If first-line regimen fails, then such individuals should be referred for allergy testing, as in experience such patients are successfully treated with salvage regimens that contains amoxicillin.

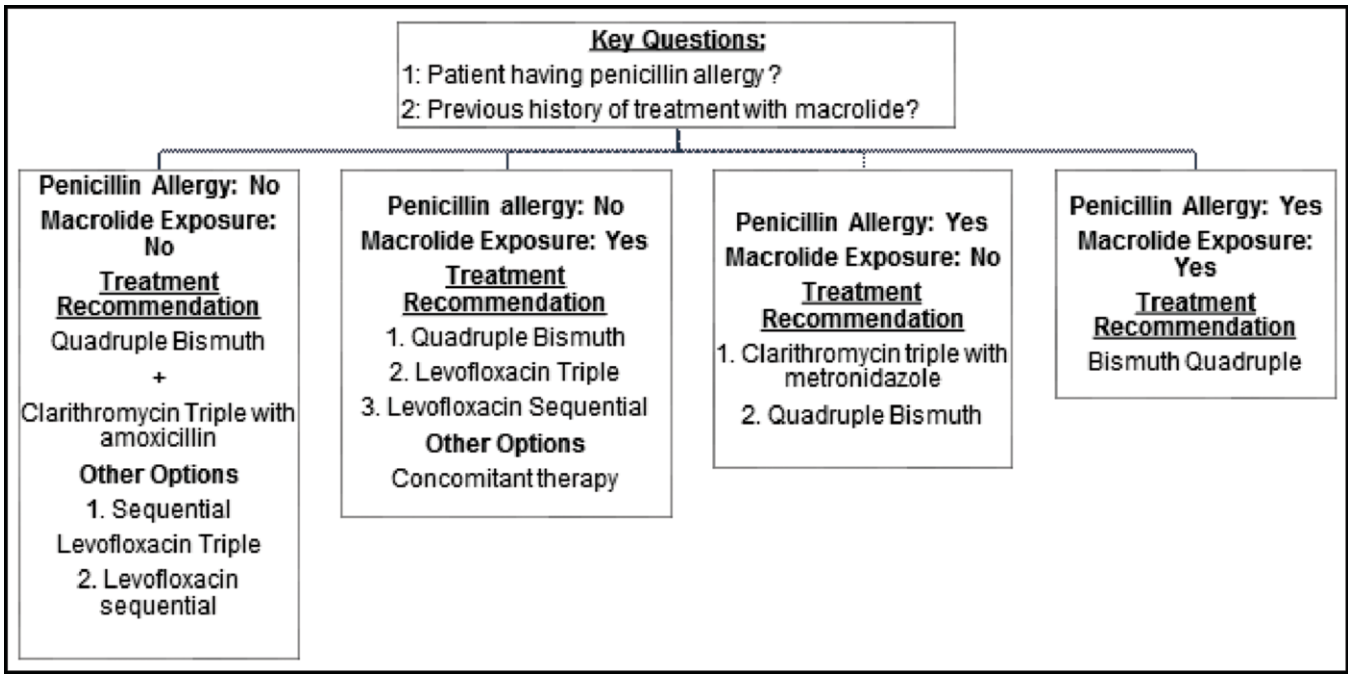

Figure-3: Treatment Options for Penicillin Allergic Patients.[3]

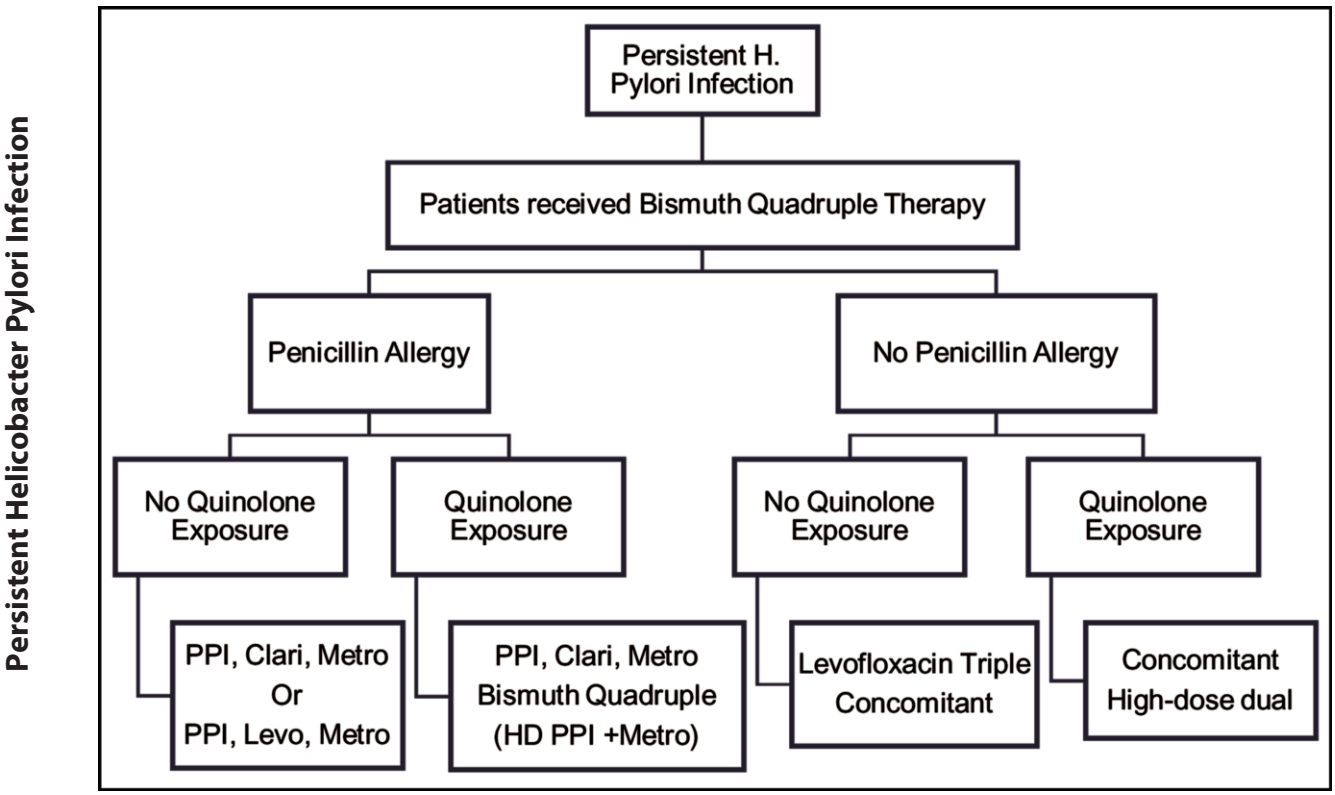

Figure-4: Persistent H. Pylori infection when a patient received Bismuth Quadruple Therapy.[4]

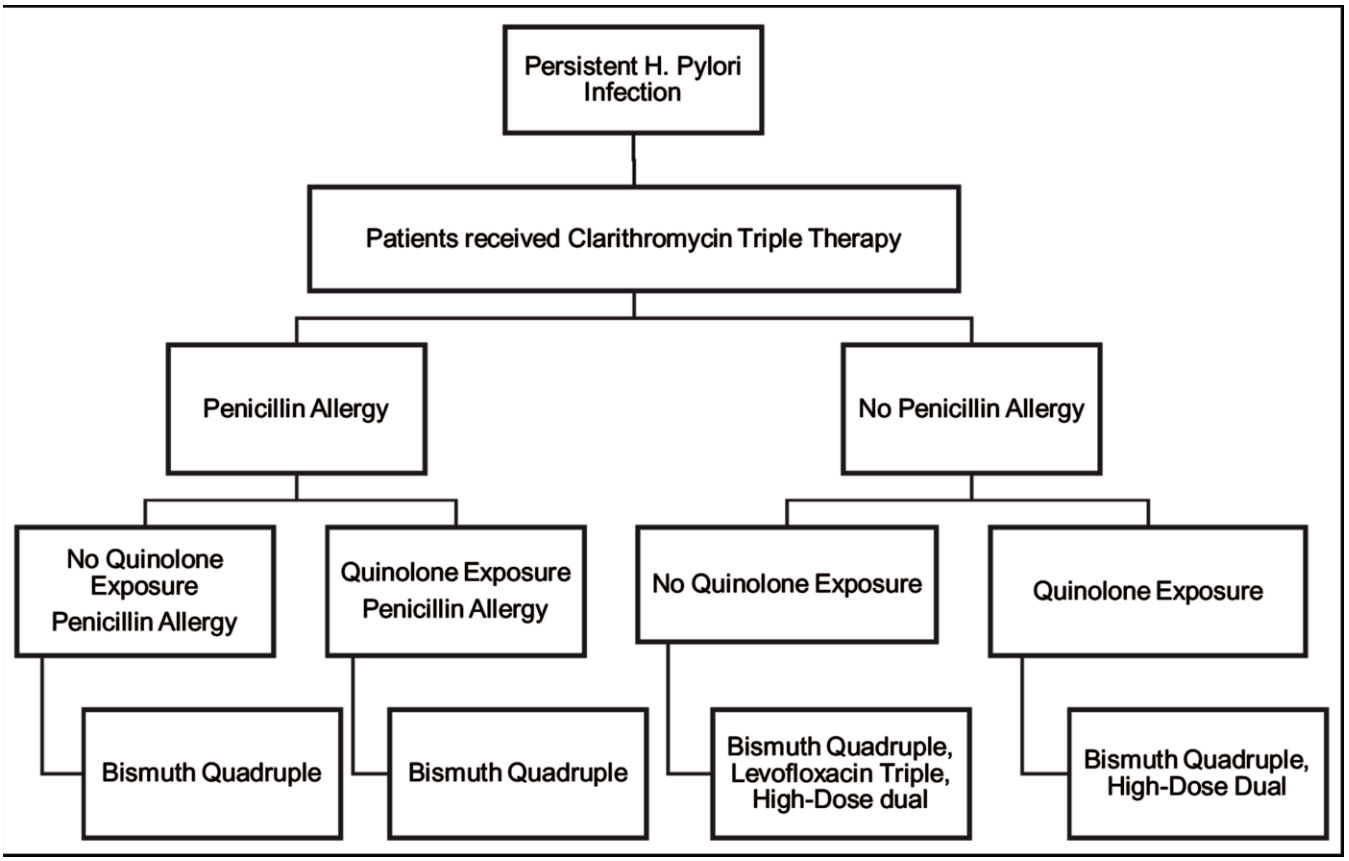

Figure-5: Persistent H. Pylori infection when a patient received Clarithromycin Triple Therapy.

Asymptomatic Patients to Treat or Not to Treat

• According to the American College of Gastroenterology guidelines, there is scarce evidence to justify routine testing. In the case of positive test findings, should be treated even if there are no symptoms.[8]

Post-treatment Testing

• Regular testing is frequently done after H. pylori therapy to document eradication. (PPI must be stopped 10-14 days before the procedure.)

• A urea breath test or a stool antigen test are commonly used. (PPI must be stopped 10-14 days before the procedure.)

• Blood tests aren't advised for testing because the antibody detected by a blood test can remain in the blood for up to four months following therapy, even though the illness is no longer present[12]

The Role of Potassium Competitive Acid Blockers (P-CABs) in the Treatment of Helicobacter pylori

Mechanism of Action

Binds to potassium ions reversibly and inhibits H+ K+ ATPase enzymes, hindering acid formation. With a dose-dependent effect on acid production, it has a quick onset of action. They have an immediate duration of action and decreases acid production due to a continuous peak in plasma concentration; also, moreover no proton pump activation is required for the onset of action.[13]

P-CAB Advantages[14]

• Plasma levels are achieved quite rapidly

• Provide absolute acid secretion inhibition right from dose one

• Reversible inhibition of the gastric hydrogen potassium ATPase

• There is less variation in efficacy due to minimal / no collaboration of CYP2C19 metabolism

• They don't require enteric coating since they are acid-stable.

• Approved in Japan (PDMA) and in United States (FDA).

P-CAB Limitations

• Clinical trials are limited worldwide and locally.

• Negative effects (no long-term data is available)

• Contraindications: Concomitant use with medicines that require an acidic stomach pH for absorption (little data available).

• Pregnancy category: Not recommended

The Role of Probiotics in the Treatment of Helicobacter Pylori

When different probiotics were supplemented with H. Pylori eradication therapy, a comparison study was conducted. Out of a total of 20,215 patients, 140 were recognized (44 English and 96 Chinese). H. pylori eradication therapy included more than ten different probiotic techniques, all of which were found to be effective. In triple therapy, however, no probiotic was found to be more effective than the others.[15]

Treatment of Helicobacter pylori infection with two probiotic strains

In a randomized placebo-controlled trial, it was discovered that combining a double strain probiotic (Lactobacillus) with standard triple therapy (STT) significantly reduced H. pylori infection. L.casei was observed to be the most efficacious for H. Pylori elimination rates, and a multi-strain combination of L. acidophilus and L.rhamnosus for overall side effects.[16]

Effect of Lactobacillus ReuteriAddition on Helicobacter pylori Elimination with Clarithromycin-Based Sequential Therapy

Liaquat National Hospital did local comparison research. Patients with H. pylori infection were separated into two groups: the controlled group (those who received sequential therapy) and the interventional group (those who received sequential therapy plus Lactobacillus Reuteri). It was concluded that adding Lactobacillus Reuteri to the sequential therapy had no meaningful effect on H. pylori eradication. In contrast to traditional treatment,however it aids in the improvement and early resolution of symptoms.[17]

The Use of Saccharomyces Boulardii in Conjuncton with Quadruple Therapy for H. pylori Eradication Reduced Diarrhoea Span and Severity

A randomised controlled trial was conducted in China. Patients infected with Helicobacter pylori were separated into two groups. For 14 days, Group A received quadruple therapy as usual, whereas Group B received quadruple therapy plus saccharomyces boulardii. During this time, all problems and adverse effects were observed. All of the patients were given a Urea breath test after 4 weeks.

S.boulardii-quadruple therapy combination decreased the side effects significantly (27.8 % in group A vs. 38.5% in group B, P-value = 0.034).Similarly it was observed that diarrhoea event was also reduced (11.2 % in group A vs. 21.2 % in group B, p-value = 0.012). The administration of S. boulardii in combination with triple treatment significantly alleviated total pre-eradication alimentary symptoms.[18]

Anti-Microbial Resistance in Pakistan

Antibiotic resistance has evolved in H. pylori, as it has in many other bacteria, leading to treatment failures. Resistance can range from single-drug resistance to multi-drug resistance. Metronidazole resistance is 44 percent in Asia-Pacific, whereas clarithromycin resistance is 17 percent, levofloxacin resistance is 18 percent, amoxicillin resistance is 3%, and tetracycline resistance is 4%.[19]

The pace of resistance is multifaceted and dynamic.Metronidazole resistance is at 78% in China, levofloxacin resistance is at 56%, clarithromycin 31%, tetracycline 15%, and amoxicillin 9%. Multidrug-resistant bacteria account for 53% of all strains.[20]

Antibiotic susceptibility testing appears smart; yet challenging at the same time, including sample type — stomach biopsy via endoscopy is essential because stool samples are not optimal. Second, the order in which the samples are collected for culture is crucial. Bismuth-based products limit bacterial development, and patients must be free of PPI for at least 2-4 weeks before their endoscopy. Furthermore, growing this bacterium necessitates the use of a specialized medium and a long period of incubation in microaerophilic conditions (requiring specialized incubators). As a result, many labs do not perform culture. Advanced multiplexed-PCR-based resistance gene detection assays (line probe assays) have been introduced, and they are more sensitive and rapid, but they are only available for a few antibiotics. For example, the A2142G/C and/or A2143G, A2147G combination has good sensitivity in detecting clarithromycin resistance, as does the 16S ribosomal mutation and gyrA mutations for tetracycline and fluoroquinolone Pakistani isolates have been shown to exhibit such mutations.[21]

Cause of Antimicrobial Resistance

Increased usage of macrolides and quinolones in the general population has been linked to resistance in H. Pylori, according to studies. Antibiotics such as clarithromycin and levofloxacin are routinely used for upper respiratory tract infections in lower and middle

income countries due to the prevalence of other diseases; metronidazole is the most generally recommended antibiotic for any type of diarrhoea. The current high prevalence of resistance to first-line antibiotics in H. pylori necessitates antibiotic judiciousness in general and emphasizes the significance of antibiotic stewardship

Characterization of Domain V Mutations in Helicobacter pylori Clinical Isolates from Pakistan and Their Impact on Clarithromycin MIC

Clarithromycin resistance is usually caused by Domain V. A study was conducted in which 93 infected patients were taken and biopsies for culture were extracted. The agar dilution method was also used to determine clarithromycin resistance. As a result, H. pylori domain V exhibited a wide range of variability and demonstrated significant resistance to clarithromycin.[22]

Relationship with Antimicrobial Resistance and CagA Gene

A total of 178 strains of H. pylori were identified from the stomach biopsies of the patients having dyspepsia. Resistance patterns were discovered about the cagA gene. Mono-resistant strains were found in 89 percent of metronidazole-resistant strains, 36 percent of clarithromycin-resistant strains, 37 percent of amoxicillin-resistant strains, 18.5 percent of ofloxacin-resistant strains, and 12 percent of tetracycline-resistant strains.[23]

Analysis of Antimicrobial Resistance of H. pylori in Chinese Community with High Risk of Stomach Cancer

Metronidazole, levofloxacin, clarithromycin, amoxicillin, and tetracycline resistance rates were 78 percent, 56 percent, 31 percent, 9 percent, and 15 percent, respectively, for H. pylori. Males had a higher rate of clarithromycin resistance than females. Levofloxacin and amoxicillin resistance rates gradually increased with time.[20]

Helicobacter pylori Associations:

Helicobacter pylori Relationship with Rosacea

Multiple studies have shown an association between H. pylori and rosacea. It is discovered that H. pylori is associated to the onset of rosacea. It is suggested that rosacea patients be screened for H. pylori infection and that H. pylori-positive rosacea patients be treated with elimination treatment to increase therapeutic effectiveness.[24]

H. pylori Relationship with Chronic Urticaria

A test named H. pylori Antigen test was performed on hundred patients with chronic urticaria of unknown cause and hundred individuals who are healthy. It was discovered that 36% of the patients had chronic urticaria and that 23% of healthy people had H. pylori infection. Thirty-three (91.67%) patients had a response to eradication therapy after H. pylori were eliminated, while three (8.33%) patients showed no effect even after H. pylori elimination. Three months later, a follow-up of 33 treated individuals was done which indicated absolute urticaria abrogation in 54.5 %, partial abrogation in 18.2%, and no deveopment in 27.3 percent.[25] Testing and treatment of H. pylori can be considered after excluding other causes of chronic urticarial..

Challenges and Future Directions

Because of the growth of drug-resistant bacteria, the high risk of relapses, particularly in nations in development, and the lack of gold-standard diagnostic tools, eradicating H. pylori remains a challenge. The bacterium colonizes within the tooth plaque and the oral cavity, according to recent developments in H. pylori therapy. Factors such as the bacterium's biology, the host's biology, and problems with diagnosis, treatment, and vaccination should all be taken into account.[26]

- Many communities in poor countries lack access to a reliable source of clean water.These communities have no other choice but to use flowing water which ultimately results in H. pylori infection. Therefore, accessibility to clean water is critical to reducing prevalence.

- First-line regimens like clarithromycin tripletherapy, bismuth quadruple, sequential & levofloxacin sequential are considered to be most effective against H. pylori.

- There must be rational use of antibiotics to reduce anti-microbial resistance. Should only be consumed when it is indicated and prescribed. Self-medication must be discouraged.

- Vaccine development is currently in progress. Initial studies in animals, particularly mice demonstrated the feasibility of immunization. Human trials are yet to be started and therefore the effectiveness of it is yet unknown.

- Blood testing for H. pylori antibodies should be discouraged in high endemic areas like Pakistan.

Best Treatment Option for H. pylori

An effective H. pylori eradication therapy must be 90% effective. Therefore, the best treatment is determined by the local guidelines on antimicrobial resistance.It is not advisable to empirically treat H. Pylori without testing. If the diagnostic test for antibiotic sensitivity is not available in the area then patient needs to be referred in another facilty.

Conclusion

H. pylori has been found primarily in developing countries with poor hygiene and sanitation.The disease's fate is determined by the continual interaction of environmental, bacterial, and host variables. The ability of H. Pylori to colonise and produce disease is influenced by genetic diversity in the bacteria's virulence components.

Data on use of probiotics and substituting PPI with P-CABs with routine antibiotic regime for H. Pylori seems promising and emerging. Recently usage of P-CABs with routine antibiotics is also approved by US (FDA) for H.Pylori treatment.

H. pylori vaccine programmes must be introduced which will be the first step towards H. pylori eradication. Also reducing irrational use of antibiotics can help minimizing resistance and ultimately will be more economical in the long run.

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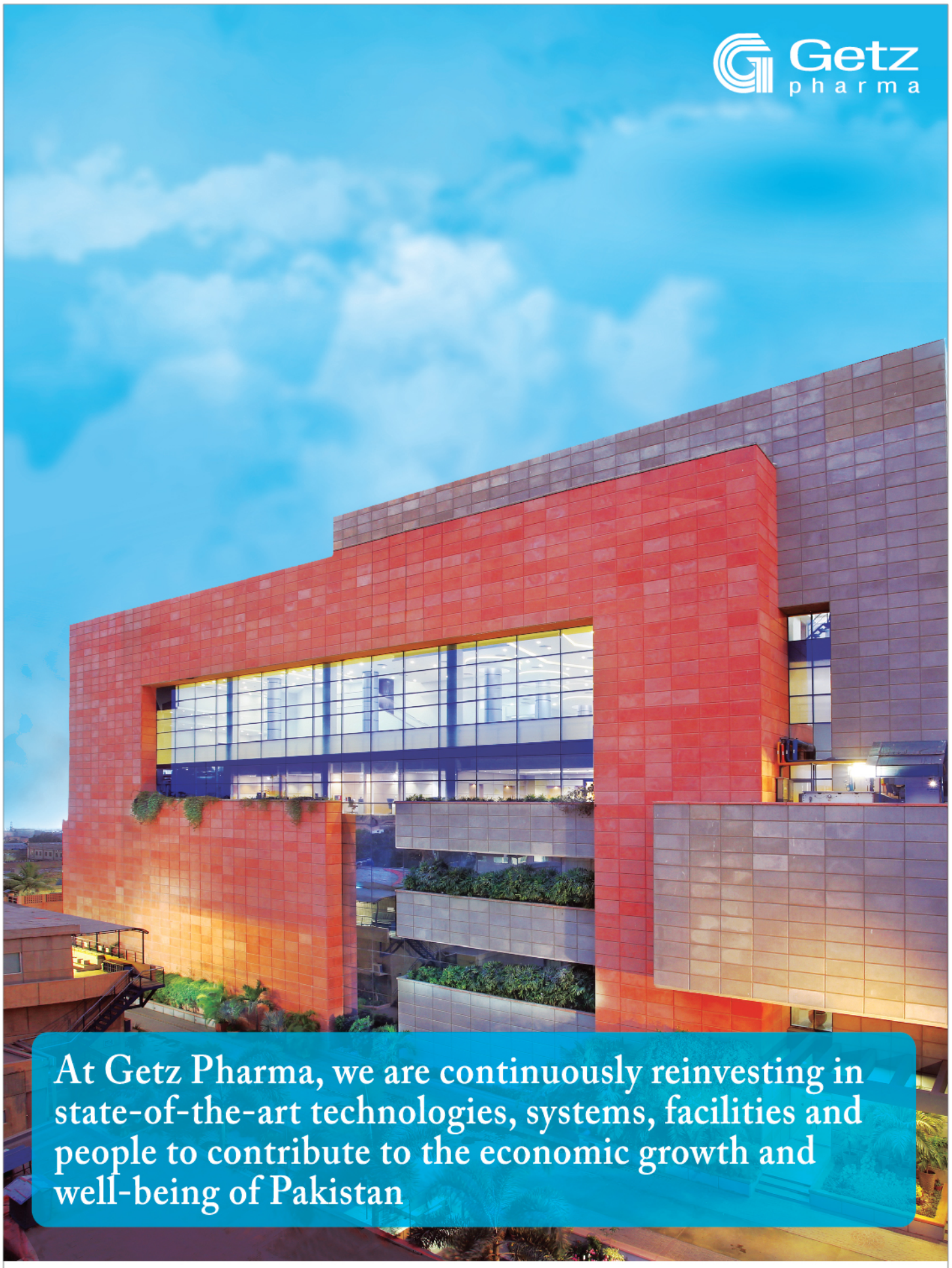

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