Ann Natl Acad Med Sci (India), 42(2): 157-168, 2006

Peptic Ulcer Disease: Managing the Paradigm Shift

Dr. M.P. Sharma
Head Deptt. Of Gastroenterology,
Rockland Hospital,
Qutub Institutional Area, New Delhi - 110016
Professor and ex Head
Department of Gastroenterology, All India Institute of Medical Sciences,
New Delhi, India

SUMMARY

Peptic ulcer is the most important organic gastrointestinal disease. The past several decades have seen dramatic advances in the diagnosis and therapy of acid related disorders. Two decades ago, almost all peptic ulcers were considered to be idiopathic, today, at least in the West, two distinct etiologies can be implicated in three fourths of patients of peptic ulcer. Helicobacter pylori is causally related to majority of cases of both duodenal and gastric ulcer both in the West and in developing countries. In developing countries almost 75% ulcers are associated with H. pylori. The second most common form of peptic ulcer is due to the use of non steroidal anti-inflammatory drugs (NSAIDs)

Management of peptic ulcers has undergone a radical change from the practice of antacids to H_2 receptor antagonists and now use of proton pump inhibitors (PPI). H. pylori eradication regimes is today the treatment of choice in peptic ulcers. By eradicating H. pylori in western countries recurrence of ulcer has been reduced tremendously in 5 years, however, in developing countries the recurrence of H. pylori infection is quite high so the ulcer recurrence is also high. The endoscopic techniques have been developed for treating complicated ulcers.

"Peptic ulcer is an epidemic during this century. It is the disease of the 20th century." This is what Sir Avery Jones had very rightly prophesised decades ago. Peptic ulcer is a disease which has its secrets unravelled over the century which has just gone by. From 1881 onwards, Billroth pioneered gastric surgery for peptic ulcer, Black swung the pendulum in 1972 by using H2 receptor blocking agents in the treatment of this disease and Marshall by implicating Helicobacter pylori as the ulcerogenic bacteria produced a revolution in the disease management. The presentation and course of the disease has not been uniform over all geographical regions and some differences exist in the disease manifestations between the tropics and other regions. This review will address key issues of peptic ulcer disease from epidemiology to management in the tropics.

Correspondence : Dr. M.P. Sharma, Head Deptt. of Gastroenterology, Rockland Hospital, Qutub Institutional Area, New Delhi-110016; Former Professor & Head, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India. Glaxo Oration 2004-2005 delivered at the Annual Meeting of NAMS at Ahmedabad, 2005.

Epidemiology

The epidemiology of peptic has been influenced by two major observations. First is the implication of H. pylori as a causative agent of peptic ulcer disease and second is the clear relationship between the ingestion of NSAIDs and gastroduodenal damage.

Peptic ulcers were rare in the 19th century and became highly prevalent in the 1950s and 1960s. Since, then peptic ulcer disease has declined in incidence, although the rate of decline has been more repaid in the developed countries as compared to developing countries. In the South East Asian countries, the incidence of ulcer disease rose as in the west, but the declined has started in the last decade and has been very gradual. Peptic ulcer disease affect males and females equally in the west while in India the men are affected more commonly than women. Both duodenal as well as gastric ulcer are equally common in the west but incidence times more commonly than women. Both duodenal as well as gastric ulcer are equally common in the west but incidence of duodenal ulcer is much more than the incidence of gastric ulcer in the tropics. The first epidemiological study on peptic ulcer in north India was conducted in 1963 (1). A population prevalence of 0.6% with a male to female ration of 1.7:1 was found in a population of 10096 urban dwellers. The ulcer was located in duodenal bulb in over two third of patients. An increased prevalence was noted in the high socio-economic groups, and dietary evaluation showed that 63% of patients were wheat eaters, thus casting doubt on the rice theory of southern India. Smoking habits were similarly in ulcer and control groups, but alcohol consumption was higher in the ulcer group. In a large country like India differences are bound to exist between regions. South India, where rice is the staple food, has a higher prevalence of peptic ulcer disease then the north (2).

Pathophysiology

The presence of gastric acid is obligatory for a peptic ulcer to form, but most patients have acid secretion within normal limits. Hypersecretion of gastric acid is rarely sufficient by itself to lead to ulceration. Currently, the most important factors in the pathogenesis of peptic ulcer disease are gastric acid secretion and Helicobacter pylori.

The following factors have a role in pathogenesis.

1. Acid secretion and duodenal ulcer

Duodenal ulcer patients a group have increased basal acid output (BAO is expressed as percentage of maximal acid output (MAO), only 10% to 20% of duodenal ulcer patients are beyond the normal range. Nocturnal gastric acid secretion is also increased in duodenal ulcer patients. Only about one third of duodenal ulcer patients have an abnormally large secretory capacity. Alternations in gastric emptying and altered duodenal pH have been implicated in the pathogenesis of duodenal ulceration, but their role has not been established. It has been seen that bicarbonate production in duodenal bulb is markedly diminished in patients with active duodenal ulcer as compared to normal individual. This leads to altered duodenal mucosal defence.

2. Acid secretion and gastric ulcer

The majority of gastric ulcers are associated with NSAID use and H.pylori infection. Resting and meal stimulated pyloric sphincter pressures are diminished in some patients with peptic disease. This permits greater duodenogastric reflux and bile and lecithin are potential gastric mucosal damaging agents. Mucosal blood flow is decreased in small group of gastric ulcer patients. NSAIDs decrease gastric mucosal blood flow in humans. It is possible that diminished blood flow may serve as a cofactor in ulceration.

3. H. pylori and ulcer disease

H. pylori infects the antral mucosa in 95-100% of patients with duodenal ulcer disease and in 70-80% of patients with gastric ulcer. The mechanism by which H.pylori leads to these disease states has not been established. Host factors as well as characteristics of bacteria interact to produce the disease state (Peura 1997, Crespo et al 2001, Nomura A et al 1994).

a) Virulence Factor

These include urease, adhesions, protease, lipase, catalase, superoxide dismutase and platelet activating factor. Strains of H.pylori posses a pathogenicity island which encodes for Cag A (cytotoxin associated gene protein) which encodes a product that promotes induction of cytokines. Approximately, 50% of H.pylori strains produce a vacuolating cytotoxin (vac A). Cag A expression was initially reported to represent an enhanced risk for the development of both gastric cancer and duodenal ulcer disease.

b) Mucosal immune responses

H.pylori induces host responses that promote inflammation and epithelial damage without conferring immunity against infection. Responses include increase interleukin-1 (IL-1), IL-6, IL-8, TNF-alpha.

c) Gastrin release

Hypergastrinemia in patients with H.pylori infection may result from a decrease in antral somatostatin content and somatostatin mRNA. There is a greater acid response to gastrin in patients with duodenal ulcer disease.

d) Mucosal Bicarbonate Secretion

Cure of H. pylori infection normalizes the decreased duodenal bicarbonate secretion in patients with duodenal ulcers.

e) Gastric metaplasia in duodenum

It has been postulated that H.pylori organisms from the stomach colonize areas of gastric metaplasia in the duodenal blub, leading to duodenitis and ulcer formation but this has not been substantiated.

4. Non steroidal antiinflammatory drugs and ulcer disease

NSAIDs are associated with approximately a five folds relative risk of developing a gastric ulcer. The incidence of new gastric ulcer in patients taking aspirin and NSAIDs is about 10-15% during the first 3 months of use. Those at risk are usually elderly patients with a history of ulcer disease, multiple NSAIDs and a high dose of these agents. Duodenal ulcers also occur as a result of NSAID use, but generally less frequently then gastric ulcers.

NSAIDs induce mucosal injury by direct topical injury and systemic effects mediated by prostaglandin depletion. Topical damage is because of 'Ion trapping' whereby the NSAIDs being weak organic acids their intracellular drugs concentration is higher then the outside. This ion trapping allows direct cellular injury, NSAIDs also directly attenuate the hydrophobic properties of systemic effects of NSAIDs are due to prostaglandin depletion. Inhibition of cyclooxygenase with a resultant decrease in PGE, PGE2 and PGI2 are though to be the most important mechanism of action. This leads to decreased mucin secretion, decreased in bicarbonate secretion, decreased surface active phospholipid secretion and decreased epithelial cell proliferation.

5. Smoking and Ulcer Disease

Peptic ulcer disease and smoking are strongly associated based on epidemiological and clinical studies. Cigarette smoking has also been associated with complications related to peptic ulcer disease. The mechanisms whereby smoking causes these effects are not understood. Chronic smoking increases maximal gastric acid secretion and it also acid secretion. Nicotine significantly reduces duodenal but not gastric mucosal blood flow. It also inhibits duodenal and pancreatic bicarbonate secretion.

6. Genetic factors

The concordance for peptic ulcer among identical twins is approximately 50% and is increased among non identical twins, although not to the same degree. The lifetime prevalence of developing ulcer in first degree relative of ulcer patients is about three fold greater then that in t he general population.

Clinical Course

Peptic ulcer disease is a chronic disease with frequent relapses and remission. Eradication of H.Pylori or the use of long term acid suppression diminishes the risks of complications and lowers the relapses rate. Epigastric pain is the predominant symptom in 60-80% of subjects. Typical pain of duodenal ulcer occurs 1-3 hours after meals and frequently awakens the patient at nigh. The discomfort is relieved by food or antacids and is sometimes described as a burning hunger pain or a vague discomfort. Ulcer symptoms are typically episodic with relapses lasting upto 2 week. Gastric ulcer is often asymptomatic, particularly in elderly patients taking NSAIDs. The pain of gastric ulcer is not helped by food and symptoms are also less likely to show periodicity. Vomiting in ulcer disease may signify gastric outlet obstruction as a consequence of chronic ulceration or pyloric obstruction. Weight loss may occur in patients with peptic ulcer, particularly gastric ulcer. Symptoms found to have discriminate value of ulcer are night pain and relief from pain with food, mild or antacids.

Complications of ulcer disease include haemorrhage, penetration and obstruction. Haemorrhage is the most common complication followed by perforation. Duodenal ulcers tend to perforate anteriorly while gastric ulcer tends to perforate along the anterior wall the lesser curvature of the stomach.

H. pylori and Peptic ulcer disease

Epidemiology

H. pylori is found in a substantial proportion of the population. It remains among the most universal of infection. Oral-oral and oral – fecal transmission accounts for most, if not nearly all, cases of infection. H.pyori infection has declined rapidly in all developing countries, which probably has contributed to declines in duodenal ulcer disease and gastric cancer. Several studies have reported H.pylori prevalence of at least 90% of persons with duodenal ulcer. However it now appears that the importance of H.pylori in ulcer disease has been overstated. The implication for epidemiologic studies is that a substantial minority of ulcers thought to be purely attributable to H.pylori must have other causes. The reported prevalence of H.pylori infection in healthy or asymptomatic persons in India varies from 31% to 84% and this depends on age, socio-economic class, housing and sanitation, rural versus urban dwelling and the method used for diagnosis. H. pylori is supposed to be an infection of the childhood in India, and the majority of the population in India is already exposed by the age of 20 yrs. In India, Gill et al showed that the prevalence of IgG and IgA antibodies to the organism was 22%, 56% and 87% and 48%, 58% and 83% in the 0-4, 5-9 and 10-19 years age groups, respectively; thereafter it remained constant up to the fifth decade with a fall in later decades.(3)

Prevalence in disease states

The strongest association of H. pylori has been with peptic ulcer disease. H pylori has been reported to be present in 64-90% of Indian patient with duodenal ulcer. The prevalence of H.pylori in other gastroduodenal disease in Indian patients is gastric ulcer; 50-65% gastric cancer; 38-62% and no ulcer dyspepsia; 42-74%.

Strain characterization

Indian strains of H.pylori seem to be distinct as compared to H. pylori strains in West. PCR tests with a focus on putative virulence genes indicated that 80-90% of strains in Calcutta carried the cag pathogenicity island and potentially toxigenic vacAs1 alleles of the vacuolating cytotoxin gene (vac A) independent of disease status. This is higher than in the West (where cag A and vacA s1 genotypes are disease associated) but lower than in East Asia. The ice A2 gene was weakly associated with disease in Calcutta strains, whereas in the West the alternative but unrelated ice A1 gene at the same focus is weakly disease associated. In a study from Delhi, it was seen that cag A status was not helpful in predicting non ulcer dyspepsia from peptic ulcer disease.

Diagnosis of H. pylori infection

The preferred schema for H.pylori infection is diagnosis, treatment and confirmation of cure. Choosing the appropriate H. pylori test depends on several factors, such as indications for endoscopy, previous H. pylori therapy current or recent medications, and accuracy as well as coast of available testing alternative. The diagnosis of H.pylori infection can be based on invasive test which are endoscopy related tests, non-invasive non endoscopic tests.(4,5,6) No

single test is considered as the gold standard. For a definitive diagnosis consensus of two or more tests is considered as positive result for the diagnosis of H.pylori. Although this also depends on whether this question is being asked in a clinical practice setting or research setting.

Endoscopy based tests

Rapid urease test

With the observation that H. pylori is a strong urease producer, urease has been used as a marker for H. pylori in rapid urease tests and urea breath test. Rapid urease test is the cheapest and most easily available of all available tests. It is based on the principle the H.pylori produces an enzyme urease which cleaves urea into ammonia and carbon dioxide which will turn the pH indicator solution red from yellow. A positive result is available from a few minutes to 24 hours. Commercially available kits are available. However, at most centres an in-house prepared solution is used. This has been validated at most centres in India. The sensitivity and specificity of this test are 95% and 90% respectively. For maximal speed, urease tests should be performed at room temperature with rewarmed media because of the enzyme's higher activity at increased temperature. All biopsy based methods suffer from the patchiness problem. For example one biopsy specimen can be colonized heavily with H. pylori whereas a second biopsy sample 1 cm away can reveal hardly any organisms.

Culture

H. pylori is a fastidious organism to culture, hence it is the most difficult test to perform. It is considered to be the gold standard for the diagnosis of H. pylori however it suffers from the disadvantage of poor sensitivity. The sensitivity at centres with special expertise in this technique has been reported to be 60-90%. Hence, it is not recommended as a routine diagnostic procedure. Culture is required if antibiotic sensitivity is needed or for isolating the strain prior to molecular biology studies. Microbiology laboratories are interested in culturing H. pylori a) for diagnostic purposes b) to establish antibiotics susceptibility of isolates c) to identify potential virulence factors and d) to investigate microbial host- cell interactions. The disadvantages of this technique are a) requirement of special conditions for specimen transportation b) the use of expensive and complicated media with special conditions for maintenance and c) need for special incubation conditions.

Histology

Due to poor yield of culture, histology is considered to be the gold standard for the diagnosis of H.pylori. Although histology may be considered as a gold standard the reliability of detecting H. pylori infection depends on the site, number and size of gastric biopsy specimens. Special stains like Warthin Starry and modified giemsa give better results then Haematoxylin- eosin.

Crushed smear sand imprint cytology

Crushed smear and imprint cytology are done with the aid of antral biopsy specimen. They are as accurate and convenient as histology. The sensitivity and specificity of histology touch smear RUT

and brush cytology of endoscopic antral biopsy from 49 patients of duodenal ulcer was evaluated in a study from Delhi and it was found that best method for diagnosis of H. pylori is a combination of the rapid urease test or brush cytology with histology. In this study it was also observed that brush cytology or touch smear are diagnostic test of choice if a single test is desired.

Polymerase chain reaction

The use of polymerase chain reaction (PCR) for successful detection and characterization of H. pylori from clinical and environmental specimens has been well documented and is being used widely. Using urea primer on antral biopsy specimens PCR has been used for the diagnosed of H. pylori. However, PCR cannot distinguish between viable and nonviable organisms. In daily clinical practice, PCR does not have to be performed to establish H. pylori infection.

Non invasive tests

Urea breath test

The urea breath test is the non-invasive method of choice to determine Helicobacter pylori status. The test is based on the organism's urease activity, which liberates carbon dioxide from urea and produces ammonia to buffer its acidic environment. Ingestion of labelled urea results in production of labelled carbon dioxide which then can be detected in breath. There are two labelled tests available: C-13 and C14 urea breath test. C13 is non radioactive is minimal at the doses used. It is a highly sensitive and specific test with a diagnostic accuracy of 93%. Moreover, it offers the advantage of being a global test i.e. there is no sampling error as seen in endoscopic tests. The most important advantage of UBT is that it obviates the need for antral biopsies to confirm eradication of H.pylori after completion therapy.

Serology

Serology testing is the commonest method on non-invasive diagnosis of H.pylori. Serology is the best method for epidemiological studies but cannot distinguish between past and present infection. Serology detects the presence of IgG and IgA antibodies against H.pylori antigens in the serum. ELISA using a commercial kit has a high sensitivity of 95-100%. These are excellent for use in primary health care setting. Serologic testing is more definitive and differentiating if the antigenic epitopes of H. pylori can be differentiated based on antigenic epitopes that specifically associated with gastric cancer, peptic ulcer and non ulcer dyspepsia.

Choice of test

The choice of a diagnostic test will depend on the clinical situation for which it is required. The selection test at different centres also reflects personal preferences, facilities and skill available and the purpose of the study.

Epidemiological studies

ELISA should be used in this situation.

Diagnosis in a clinical practice

If endoscopy is planned then any of the endoscopic tests like RUT or histology will be sufficient. To reduce the cost, one sample can be used for RUT and the other sample

preserved. If RUT is negative at 24 hours, the second sample should be sent for histology. The biopsies should be taken endoscopically from two sites: the gastric antrum and the corpus. If endoscopy is not planned then urea breath test is a good alternative.

Diagnosis after therapy

Test for H.pylori are done minimum of 4 weeks after completion of therapy. In cases of duodenal ulcer where symptomatic relief has been gained, C14 urea breath test is sufficient to demonstrate eradication of organism. For clinical trials a combination of two of the following tests can be used: RUT, histology or urea breath test.

Strategies for successful eradication

Treatment

Similar to any bacterial infection, the treatment of H. pylori infection is based on the use of antimicrobial agents. An adjuvant therapy is needed and until now the best adjuvant therapy has comprised drugs that increase the pH of the stomach (i.e. antisecretory drugs and especially proton pump inhibitors (PPI).

Indications for treatment

Eradication of H.pylori cures peptic ulcer disease and conversely relapses of peptic ulcer disease are associated with reappearance of H. pylori. This is the basic concept for which H. pylori eradication had been advocated. In 1994, National Institutes of Health consensus development conference had recommended eradication of H. pylori in all cases of duodenal ulcer infected with H. pylori. Subsequently, European H. pylori study group, American College of Gastroenterology and 1997 Asia Pacific working party had also recommended eradication of H. pylori in peptic ulcer disease. Eradication therapy was also recommended in all patients with low grade gastric MALT lymphoma with coexisting H. pylori. Eradication is not recommended in non ulcer dyspepsia with or without antral gastritis. In a bleeding peptic ulcer disease or a past history of ulcer with proven H. pylori infection eradicating therapy should be given.

First Line Therapy

The drugs effective against H. pylori are bismuth salts (colloidal bismuth sub citrate, bismuth subsalicylate), metronidazole, Tinidazole, secnidazole tetracycline, amoxicillin, Clarithromycin, azithromycin, omeprazole, lansoparazole, quinolones and ranitidine bismuth citrate.(7-12). However, a single drug is not effective and moreover it promotes drugs resistance. Hence, at present a three or four drug regimen is indicated. The regimen should include a proton pump inhibitor and two antibacterials in triple therapy while in quadruple therapy it should contain protein pump inhibitor, bismuth and two antibiotics. The time of therapy should be 14 days. As it has been seen that 7 days therapy does not produce optimal eradication rates. No single therapy can be recommended for all of India as there are wide variations in the resistance patterns in different parts of India. The following regimens may be considered:

- PPI (Lansoprazole 30mg BD, omeprazole 20mg BD) + amoxicillin 1 gm twice daily + clarithromycin 500mg twice daily for 14 days.

- PPI+amoxicillin 1 gmBD/clarithromycin 500mgBD+tinidazole 500mgBD for 14 days
- Colloidal Bismuth subcitrate 240mg BD+PPI+ amoxycillin/clarithromycin + tinidazole for 10-14 days

Factors Influencing outcome

Factors linked to treatment:

1. Dose of clarithromycin: Increasing the dose of clarithromycin to 1-1.5mg/day improves cure rates.
2. Duration of treatment: the optimal duration of treatment remains controversial. It has been shown that better cure rates are achieved for longer treatment duration: 14 days greater than 10 days, greater than 7 days.

Factors linked to strains:

1. Resistance of H.pylori to antimicrobial agents
2. Strain type

Factors to patients:

1. Geographical region
2. Patient compliance

Second Line therapies

The choice of the second line treatment largely depends on the treatment which was used initially. If a clarithromycin based regimen was used, a metronidazole based regimen should be used and vice-versa as acquired bacterial resistance to metronidazole and clarithromycin primarily results from previous treatment failure.

Quadruple therapy (i.e. PPI twice daily, colloidal bismuth subcitrate 120mg four times a day, tetracycline 500mg four times a day and metronidazole 500mg three times a day) has been recommended as the optimal therapy in several guidelines. A seven day treatment duration seems to be sufficient and increasing the duration does not increase the efficacy. In non responders, if the initial therapy has been metronidazole based then rescue therapy should be non metronidazole based. And if the first line of therapy had been non metronidazole based then either a quadruple drug regimen should be used or the length of therapy should be increased to a minimum of 14 days. Patient compliance also needs to be monitored rigorously in such cases. Testing for eradication needs to be done in patients with relapse of duodenal ulcer, complicated duodenal ulcer and patients with gastric ulcer when ulcer healing needs to be documented. Newer compounds currently being evaluated for eradication of Helicobacter pylori include macrolides other than clarithromycin, fluoroquinolones, rifamycin derivatives and others.

Macrolides

Azithromycin is able to reach high gastric concentrations persisting for several days and therefore may be administered at a dose of 500mg once daily for three days during a seven day triple eradication therapy. Eradication rates ranging from 28% - 93%59 have been reported for regimens employing this antibiotic. The absorption of azithromycin is markedly reduced when administered with food, which may account for the low eradication rates. In treatment regimens in which azithromycin was given to fasting patients,

cure rates were in the range of 86%-93%. Spiramycin is a well tolerated macrolide. It has shown eradication rates of 89%-91% when administered for 10 days with metronidazole and bismuth subnitrate or ranitidine bismuth subcitrate.

Fluroquinolones

Levofloxacin is being evaluated for its role in eradication of H.pylori. A therapeutic regimen comprising levofloxacin 500mg daily plus rabeprazole and either amoxicillin or tinidazole for 1 week has been found to promote eradication of H. pylori in 90%-92% of treated patients.

High dose dual therapy

PPI and amoxicillin dual therapy widely used in the early 1990's was abandoned because of the inconsistent results and an inferior eradication rate compared to the PPI based triple therapies. As compared to macrolides and metronidazole, amoxicillin never reaches high concentration in the gastric mucosa. Thus an alternative would be to given high doses of omeprazole (40mg 3 times a day) and amoxicillin (1 gm 3 times a day). 80% eradication rate has been reported in initial pilot studies.

Rifabutin

Rifabutin is a rifamycin derivative, which has been used in 'rescue' triple therapy for patients failing to respond to standard regimens for H.pylori eradication. Both quadruple and triple drug regimens employing rifabutin 150mg daily promoted eradication in 66.6% of cases, while the eradication rate was 86.6% ($p<0.025$) in the group employing rifabutin 300mg daily. The study indicates rifabutin is more effective than the so-called second line quadruple therapies, but it needs to be confirmed in futures studies.

Nitazoxamide

Nitazoxamide is a nitrothiazolamide with similar properties as nitroimidazoles but it has the advantage of being well tolerated and does not select resistant H. pylori strains. An eradication rate of 83% was obtained in a dose ranging trial of nitazoxamide with omeprazole.

Ketolides

Ketolides are macrolide derivatives developed to be active against macrolide resistant bacteria. Trials for their effectiveness against H.Pylori are yet to be conducted.

New drugs based on genomics

The complete genomic sequencing of two H.pylori strains may change the present approach to H.pylori eradication. Numerous genes are specific to H. pylori and are common to all strains. Post genomic methods allow an effective screening of these genes and once their vital role is confirmed by mutagenesis they can be screened against thousands of small molecules. This would lead to the development of active drugs, which specifically target certain functions of the bacterium.

Recurrence after eradication

Recurrence is defined as tests for H.pylori which were negative 4 weeks after eradication, becoming positive again. Recurrence can be due to recrudescence of

reinfection. Recrudescence is a pre-treatment strain of H.pylori which was suppressed by treatment and was undetectable 4 weeks after treatment, becoming detectable at a later stage. Reinfection is infection by another strain of H.pylori which infects after the original strain of H.pylori has been eradicated completely. Recrudescence is most likely to occur during the first 12 months after apparent eradication whereas reinfection my account for recurrence after this period. Data from India on reinfection are scarce. Very few Indian studies are available. In three studies reinfection rate was 16% per patient year follow up (range 11%-40%). In the fourth study H.pylori clearance (colonization status 4 weeks after therapy) was studied rather than eradication (colonization status 4 week after therapy) and it was found to be 59% at 3-6 months suggesting that it was due to recrudescence. The ulcer relapse rates were 17% during an average follow up of one year (13,14). This is in contrast to developed countries where the reinfection rate is 0-3% per patient year follow up. Relatively higher reinfection and ulcer relapse rates reported from India could be either due to genetic susceptibility or reexposure to H.pylori. There could be methodological flaws like improper assessment of H.pylori eradication rates as only one test like rapid urease test was used to document eradication in most studies.

Drug resistance in H.pylori infection

Drug resistance appears to be one of the main reasons for failure of therapy. Resistance is more frequent to metronidazole and clarithromycin. There are some reports of resistance to amoxycillin and tetracycline also (15).

Resistance to imidazoles

In Lucknow, metronidazole resistance was found in 66% of cases. In Mumbai, Mhaskar *et al* found resistance to both metronidazole and tinidazole in 100% of the cases. Another study from Mumbai reported resistance to metronidazole in 16% of the cases. In Hyderabad resistance to metronidazole was seen in 17% of the cases. Data collected from seven centres in India showed that 70% of the strains were resistant to metronidazole. Preliminary data shows that resistance to metronidazole from strains isolated in Delhi is about 100%. In Calcutta, 90% of the strains are resistant to metronidazole. Adding proton pump inhibitors to regimens containing metronidazole appears to overcome the problem of metronidazole resistance in vivo. The resistance can also be overcome by using a quadruple (bismuth containing) regime instead of triple regime.

Resistance to clarithromycin

Mhaskar *et al* found 91% of the strains to be resistant to clarithromycin. All strains from Mumbai which were resistant to metronidazole, tinidazole and clarithromycin were sensitive to quinolones. In 3-4% of the cases combined clarithromycin and metronidazole resistance occurs.

Antimicrobial resistance in vitro may not always translate into low eradication rates with triple or quadruple therapies. Various antibiotic combinations may have synergistic effect that may not be apparent when components are tested alone. A strain found to be metronidazole resistant in vitro might under in vivo conditions may prove sensitive through unknown mechanisms.

REFERENCES

1. Chuttani HK, Wig KL, Chablani TD, *et al* (1963). Epidemiology of peptic ulcer: prevalence of peptic ulcer in an urban community in Delhi. *Ind J Med Res* **55**:1121.
2. Tovey FI, Jayaraj AP (1990). Peptic ulcer in India. *Gut* **31**:123-4.
3. Gill HH, Desai HG. (1993). Editorial: Helicobacter pylori and gastroduodenal disorders in India-lessons from epidemiology. *J Clin Gastroenterol* **16**:6-9.
4. Saksena S, Dasarathy S, Verma K, *et al* (2000). Evaluation of endoscopy based diagnostic methods for the detection of Helicobacter pylori. *India J Gastroenterol* **19**:61-3.
5. Ahuja V, Bal CS, Sharma MP. (1998) Can the C-14 urea breath test replace follow-up endoscopic biopsies in patients treated for Helicobacter pylori infection? *Clinical Nuclear Medicine* **18**:330-2.
6. Sharma MP. (2000) Diagnosis of Helicobacter pylori infection: who should be tested with intention to treat? *Indian J Gastroenterol* **19**(suppl1):S36.
7. Gupta VK, Dhar A, Srinivasan S, *et al* (1997). Eradication of H.pylori in a developing country: comparison of lansoprazole versus omeprazole with norfloxacin in a dual therapy study. *Am J Gastroenterol* **92**:1140-2.
8. Ahuja V, Dhar A, Bal C, *et al* (1998). Lansoprazole and secnidazole with Clarithromycin, amoxicillin or pefloxacin in eradication of Helicobacter pylori in a developing country. *Alimentary Pharmacol Therap***12**:551-5.
9. Kumar D, Ahuja V, Dhar A, Sharma MP. (2001) Triple versus quadruple drug regime for eradication of H.Pylori in patients with duodenal ulcer-results of a prospective randomised trial. *Indian J Gastroenterol* **20**:191-4.
10. Ahuja V, Bhatia V, Dattagupta S, Raizada A, Sharma MP. (2005) Efficacy and tolerability of rifampicin-based rescue therapy for Helicobacter pylori eradication failure in peptic ulcer disease. *Dig Dis Sci.* **50**(4):630-3.
11. Bhatia V, Ahuja V, Das B, Bal C, Sharma MP. (2004) Use of imidazole-based eradication regimens for Helicobacter pylori should be abandoned in North India regardless of in vitro antibiotic sensitivity. *J Gastroenterol Hepatol* **19**(6):619-25.
12. Chaudhary A, Ahuja V, Bal CS, Das B, Pandey RM, Sharma MP. (2004) Rank order of success favors longer duration of imidazole-based therapy for Helicobacter pylori in duodenal ulcer disease: a randomized pilot study. *Helicobacter* **9**(2):124-9.
13. Ahuja V, Sharma MP. (2002) Recurrence of H. Pylori after successful eradication. *Gastroenterology* **123**: 2: 653-4.
14. Dhar A, Sharma MP. (1997) Lacunae in data on Helicobacter pylori from India. *Indian J Gastroenterol* **16**(suppl 1): S13-15.
15. Thyagarajan SP, Ray P, Das BK, Ayyagari A, Khan AA, Dharmalingam S, Rao UA,Rajasambandam P, Ramathilagam B, Bhasin D, Sharma MP, Naik SR, Habibullah CM. (2003) Geographical difference in antimicrobial resistance pattern of Helicobacter pylori clinical isolates from Indian patients: Multicentric study. *J Gastroenterol Hepatol* **18**(12): 1373-8.