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Helicobacter pylori Eradication: Decision Making in Clinical Practice

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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. 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 rapid in the developed countries as compared to developing countries. Susser and Stein introduced the key concept of birth cohort (i.e. those born during the same time period) to explain this phenomenon[1]. They have shown that the annual death rate for duodenal ulcer was greatest in the cohort of population in the final quarter of the 19th century in the Western society. This suggested that some environmental factor operated on this cohort of persons and that the influence of this factor has since declined. *Helicobacter pylori* infection appears to be the possible explanation for this cohort damage.

The first epidemiological study on peptic ulcer in North India was conducted in 1963[2]. A population prevalence of 0.6% with a male to female ratio of 1.7 : 1 was found in a population of 10,096 urban dwellers. The ulcer was located in the duodenal bulb in over two-thirds of patients. A higher prevalence was seen in higher socio-economic group and dietary evaluation showed that 63% patients were wheat eaters, thus disproving the rice theory of southern India. Smoking habits were similar in ulcer and control groups while alcohol consumption was higher in the ulcer group. In a large country like India differences exist between the northern region and the southern parts. South India which uses rice as the staple diet has a higher prevalence of peptic ulcer disease. The patients present at a younger age and the presenting symptom is obstruction rather than perforation or hemorrhage[3]. On comparison of the clinical presentation of duodenal ulcer in the 80's vs the 90's it is seen that day time pain continues to remain a universal phenomenon while the prevalence of night time pain seems to be higher in the present era[4]. This may be because of a change in a lifestyle of patients with longer working hours and increased stress. Similarly the incidence of presentation with complications in the form of GI bleed seems to be higher in the present era. This may be a result of neglect of early symptom of pain. There has been a rapid rise in incidence of ulcer disease in the early 20th century and this phenomenon has been seen globally, but in the western countries, over the last three decades the incidence of ulcer disease has shown a rapid decline. In the South East Asian countries, the incidence of ulcer disease rose as in the west, but the decline has started in the last decade and has been very gradual[5]. Peptic ulcer disease affects males and females equally in the west while in India the men are affected 18 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. Placebo healing rates are as high as 75% in Mexico and can be as low as 5% in Philippines. Prevalence of *H. pylori* also shows disparity between the western and the eastern countries. *H. pylori* can be considered a 'submerging' pathogen rather than an 'emerging' pathogen as the prevalence of this infection is showing a decline. In the east the acquisition of this disease occurs at a much younger age and by adulthood most of them are infected. In the west, peak incidence of infection occurs in the adult age.

Currently, the most important factors in the pathogenesis of peptic ulcer disease are gastric acid secretion and *Helicobacter pylori (H. pylori).* Besides that NSAIDs play a major role in pathogenesis of non *H. pylori* associated peptic ulcer disease.

The prevalence of *Helicobacter pylori* infection in the Indian population ranges from 31 to 84%[6]. As in the west, a strong association has been noted between *H. pylori* infection and peptic ulcer disease. The reported prevalence of *H. pylori* infection from Indian centers in patients with duodenal ulcer, gastric ulcer, gastric cancer, and non-ulcer dyspepsia ranges from 64-90%, 50-65%, 38-62%, and 42-74%, respectively[7].

The natural history of ulcer disease was a different story before recommendations for *H. pylori* eradication were being practiced. In a study, 125 patients with endoscopically healed duodenal ulcer were followed up for a mean period of 1.5 years by endoscopy at 3 months intervals or on recurrence of symptoms. Endoscopic relapse of duodenal ulcer was found in 45% of patients of whom almost all were symptomatic relapses. 10% of patients had more than two relapses and UGI bleed occurred in 2.5%[8]. The most effective treatment for healing of peptic ulcer was proton pump inhibitor as a controlled trial of 40 mg of Famotidine Vs 20 mg of omeprazole showed that at 2 weeks a significant difference was found in the healing induced by omeprazole which equalized at 4 weeks of therapy. Both day time pain and night time pain were relieved in a significantly higher number of patients in the omeprazole group[9].

Subsequently, the NIH consensus in 1994 was that eradication therapy should be given to all patients with gastric or duodenal ulcers and presence of *H. pylori*, regardless of whether the ulcer disease is active or chronic. The first Indian national workshop in 1997 recommended treatment of *H. pylori* in patients with duodenal ulcer, gastric ulcer and low grade gastric lymphoma. Asia Pacific consensus in 1997 also recommended the treatment of all gastric and duodenal ulcers infected with *H. pylori*. It also recommended eradication of *H. pylori* in low grade gastric lymphoma and in planned long term NSAID therapy[10].

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 Institute 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[11-16]. However, a single drug is neither 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 30 mg BD, omeprazole 20 mg BD) + amoxicillin 1 gm twice daily + clarithromycin 500 mg twice daily for 14 days.
- PPI + amoxycillin 1 gm BD/clarithromycin 500 mg BD + tinidazole 500 mg BD for 14 days.
- Colloidal Bismuth subcitrate 240 mg BD+PPI+ amoxicillin/clarithromycin + tinidazole for 10-14 days.

Factors Influencing outcome

Factors linked to treatment:

1. Dose of clarithromycin: Increasing the dose of clarithromycin to 1-1.5 mg/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 linked 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 120 mg four times a day, tetracycline 500 mg four times a day and metronidazole 500 mg 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 500 mg once daily for three days during a seven day triple eradication therapy. Eradication rates ranging from 28-93% 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.

Fluoroquinolones

Levofloxacin is being evaluated for its role in eradication of *H. pylori*. A therapeutic regimen comprising levofloxacin 500 mg 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 a 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 (40 mg 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 150 mg daily promoted eradication in 66.6% of cases, while the eradication rate was 86.6% ($p < 0.025$) in the group employing rifabutin 300 mg 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 pretreatment strain of *H. pylori* which was suppressed by treatment and was undetectable 4 week 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[17-18]. This is in contrast to developed countries where the reinfection rate is 0-3% per patient year followup. Relatively higher reinfection and ulcer relapse rates reported from India could be either due to genetic susceptibility or re-exposure 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[19].

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 centers 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 which components are tested alone. A strain found to be metronidazole resistant in vitro might under in vivo conditions may prove sensitive through unknown mechanisms.

Special Problems in the Indian Context

Peptic ulcer disease differs in the tropics to some extent[20].

The decline in incidence of ulcer disease has started recently only in the tropics. Ulcer disease is seen more commonly in younger males with the predominant site being duodenum. The acquisition of *H. pylori* infection also occurs at a younger age. Diagnostic methods—both endoscopic and non endoscopic–are equally important in the diagnosis of *H. pylori*. A combination of histology with rapid urease test or brush cytology offers the best combination. Following eradication, a non invasive test like C14 urea breath test may suffice. Strain heterogeneity is certainly present and virulence genes are not discriminatory in the tropics. There is a higher degree of antibiotic resistance with lower eradication rates of *H. pylori* as compared to the west. The recurrence rate of ulcer disease despite eradication of *H. pylori* is also higher in the tropics possibly because of reinfection.

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