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Helicobacter pylori infection in India from a western perspective

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Helicobacter pylori **is a common bacterial infectious disease whose manifestations predominately affect the gastrointestinal tract. India is the prototypical developing country as far as *H. pylori* infection is concerned and more than 20 million Indians are estimated to suffer from peptic ulcer disease. Considering the high level of medical research and of the pharmaceutical industry, one would expect that India would be the source of much needed information regarding new therapies and approaches that remain effective in the presence of antimicrobial resistance, new methods to reliably prevent reinfection, and the development of therapeutic and preventive vaccines. Here we discuss *H. pylori* as a problem in India with an emphasis on *H. pylori* infection as a serious transmissible infectious disease. We discuss the pros and cons of eradication of *H. pylori* from the entire population and come down on the side of eradication. The available data from India regarding antimicrobial use and resistance as well as the effectiveness of various treatments are discussed. Rigorous ongoing studies to provide current regional antibiotic resistance patterns coupled with data concerning the success rate with different treatment regimens are needed to guide therapy. A systematic approach to identify reliably effective (*e.g.*, 90% or greater treatment success) cost-effective regimens is suggested as well as details of regimens likely to be effective in India. *H. pylori* is just one of the health care problems faced in India, but one where all the resources are on hand to understand and solve it.**

Key words Antibiotic resistance - epidemiology - eradication - *Helicobacter pylori* - India - treatment

Helicobacter pylori is a common and important transmissible bacterial human pathogen. The prevalence of this infection varies world wide being as low as 10 per cent in developed western nations to higher than 80 per cent among the indigent populations of many developing countries. The infection primarily involves the upper gastrointestinal tract causing progressive acute and chronic gastro-duodenal inflammation. Typically these inflammatory changes are silent but clinical disease manifestations occur in approximately 20 per cent, generally after a long latent period[1]. The manifestations of *H. pylori* infection include gastritis, gastric atrophy, duodenal ulcer disease, gastric ulcer disease, primary gastric B-cell lymphoma, gastric adenocarcinoma, iron deficiency anaemia, and vitamin B12 deficiency[2-5]. There are often regional differences with regard to which clinical manifestation is predominant ranging from iron deficiency anaemia in childhood to gastric cancer in the elderly. The predominant manifestation can also evolve over time.

For example, in the first half of the 20th century there was a rapid and progressive decline in the incidence of gastric cancer in the west which coincided with a sharp rise in the incidence of duodenal ulcer.

Gastric cancer is one of the most significant outcomes of *H. pylori* infection and understandably attracts the most attention from the research community. However, in many areas, especially in tropical and semitropical countries (*e.g.*, Africa, southern India), the infection is common but gastric cancer is rare with duodenal ulcer being the dominant clinical manifestation of the disease[5-7]. Less dramatic, but no less important, is an increased susceptibility to enteric infections due to *H. pylori* gastritis-related hypochlorhydria and iron deficiency anaemia both of which can have major deleterious effects on physical and intellectual growth of children especially in developing countries[8].

H. pylori infection is typically acquired in childhood. The risk of infection is inversely related to the overall sanitary conditions and requires exposure to other infected humans. Contaminated water is often the primary mode of transmission in rural areas without reliable supplies of potable water[9,10]. However, in regions of higher socio-economic status the risk of infection best correlates with the level of household hygiene.

Outcome of *H. pylori* infections

The outcome of an *H. pylori* infection reflects a complex interplay of environmental, host and bacterial factors including the virulence of the infecting bacterial strain. There are no nonpathogenic strains of *H. pylori* as even the least virulent strains cause gastric inflammation and have been associated with peptic ulcer disease and gastric cancer. The virulence of *H. pylori* strains correlates with the intensity of the inflammatory response to the infection. Established *H. pylori* virulence factors include the *cag* pathogenicity island (cag PAI), the vacuolating cytotoxin (VacA) and the outer inflammatory protein, OipA. Host factors involved in disease pathogenesis include polymorphisms of genes that govern the host's inflammatory response (*i.e.*, a genetic predisposition to an increased response is associated with a greater risk of a clinical outcome). A genetically determined increased parietal cell mass is thought to predispose to *H. pylori*-related duodenal ulcer disease. Environmental factors also contribute to the outcome of *H. pylori* infection. This is best seen in relation to the association of *H. pylori*-related gastric cancer with diets low in fresh fruits and vegetables but high in salt and the rapid decline in the incidence of gastric cancer that paralleled dietary changes in those populations. Replacing salt/smoke with refrigeration as the primary means of food preservation and an increased intake of fresh fruits and vegetables has universally been associated with a fall in the incidence of gastric cancer among high risk populations without a change in the prevalence or virulence of *H. pylori* infections[11-14].

Should *H. pylori* be eradicated?

H. pylori is a significant human pathogen responsible for considerable morbidity and mortality and is the major cause of gastric cancer. The majority of investigators in the field believe that whenever the infection is detected, it should be eradicated[15]. However, that goal may be difficult to attain in some non-western populations. Some have hypothesized that *H. pylori* infection may even be beneficial and that eradication is not always the best option[16]. *H. pylori* is a human pathogen. Although *H. pylori* is not present in wild monkeys, its association with mankind can be traced back to the time when humans migrated out of Africa[17]. Such a long association is neither unique nor evidence of a positive benefit, at least to man. Over the centuries, man has been host to many bacterial, viral, protozoal, and helminthic pathogens. Gradually, as populations dispersed and sanitation improved, most pathogens have been lost. *H. pylori* is one of the last of those pathogens to undergo clearance associated with improvements in the standards of living. Despite its long-standing presence, *H. pylori* is not a commensal; it always causes disease (*e.g.*, progressive gastric inflammation). Commensals are very difficult to eliminate, however, with *H. pylori,* the chain of transmission is easily broken in association with improvements in hygiene and sanitation practices.

Are there adverse consequences to *H. pylori* eradication?

In epidemiology, when one variable is associated with a reduction of another (*e.g.,* a disease) it is said to be "protective". For example, populations with limited sanitation, high rates of malnutrition and early mortality have a low incidence of age-related diseases such as diabetes, stroke, and cancer. One could conclude that from an epidemiologic standpoint poor sanitation "protects" against those diseases. This would clearly be a misuse of the medical concept of "protection". However, the same approach has been used to show that *H. pylori* infection possibly "protects" against

other diseases[18]. For example, atrophic gastritis, the precursor lesion for gastric cancer, leads to low levels of gastric acid secretion (*i.e.*, it can be considered to be a biologic anti-secretory agent) and thus protects against gastroesophageal reflux disease and its dreaded complication, oesophageal adenocarcinoma[19]. It has been suggested that possibly one should not eradicate *H. pylori* because *H. pylori* infection may protect against development of oesophageal adenocarcinoma, a clear misunderstanding of the concept of protection[19-21]. Similarly, *H. pylori* infection has been suggested to protect against obesity and childhood asthma[22,23]. Childhood asthma is often thought to be related to a failure of exposure of the immune system to important environmental antigens (the hygiene hypothesis). Does *H. pylori* infection contain some of those critical antigens? The available data suggest that the presence of *H. pylori* infection is not responsible but is instead a surrogate or marker for inadequate household hygiene. Experience in rural Malaysia allowed the *H. pylori* protective hypothesis to be tested. In rural Malaysia hygiene is often poor, and enteric diseases are common, but *H. pylori* is essentially absent[24]. One would therefore expect childhood asthma to be common, gastroesophageal reflux, oesophagitis, adenocarcinoma of the oesophagus, and obesity to be significant problems. However, childhood asthma, obesity, gastroesophageal reflux, and oesophageal adenocarcinoma are all rare[19]. These data are directly in contrast to what was predicted by those who espouse dire consequences associated with *H. pylori* eradication. In terms of childhood asthma, the experience in Malaysia is consistent with the hygiene hypothesis (*i.e.*, the likelihood of environmental antigens in priming the immune system) but is direct evidence that the critical antigens are unlikely to be related to *H. pylori* infection and support the premise that the presence of *H. pylori* infections is a marker for poor household hygiene[24].

In summary, *H. pylori* is an important human pathogen and should be eradicated whenever possible. However, eradication is more complex than the simple matter of writing a prescription for antibiotics. This paper will review *H. pylori* treatment strategies and the approach to identifying the best regimens for a particular population with a special emphasis on *H. pylori* eradication in India.

H. pylori as an Indian problem

India is a vast country known for its rich history, culture and food. It is also the prototypical developing country with a vast rural population living in poverty. The prevalence of *H. pylori* in the Indian subcontinent can be as high as 80 per cent or more in rural areas. The most commonly recognized manifestation of *H. pylori* infection in India is peptic ulcer disease, particularly duodenal ulcer disease, which outnumbers gastric ulcers between 8:1 and 30:1[25]. Singh *et al*[26] calculated the point prevalence of active peptic ulcer disease at 3% with a lifetime prevalence of 9 per cent. As in other regions, the actual risk of a particular outcome from an *H. pylori* infection is predicated on the pattern of gastritis[7]. Antral predominant gastritis leaves an intact gastric corpus, poorly controlled acid secretion and promotes duodenal ulcer formation. In contrast, with pangastritis acid secretion often falls below the level needed to produce and sustain duodenal ulcer disease (*e.g.*, approximately 12 mmol/h), gastric ulcer becomes more common than duodenal ulcer and the incidence of gastric cancer rises. Finally, atrophic pangastritis is the main precursor lesion associated with gastric cancer[27].

Environmental factors, especially diet, play a role in the pattern of gastritis and this likely underlies the differences in the prevalence of *H. pylori* diseases in India. Tropical diets with plentiful fruits and vegetables year-round promote antral predominant non-atrophic gastritis and duodenal ulcer disease[5,7]. Seasonal diets where fresh fruits and vegetables are not available during the winter or dry season and food is commonly preserved with salt promote pangastritis, a lower incidence of duodenal ulcer disease and more gastric ulcers. These environmental factors are likely responsible for the higher prevalence of duodenal ulcer in the south and for the wide range in the age-adjusted incidence rate of gastric cancer (range from 2 to 57 per 100,000)[7,11,28].

The population of India is approximately 1.2 billion people. If the *H. pylori* prevalence was 60 per cent, more than 726 million individual would be infected with *H. pylori*[29]. The estimated prevalence of duodenal ulcers in India is 3 per cent and means that at least 18 million people could need anti-*H. pylori* therapy (approximately 50,000 per day if treated over one year). The enormity of the task of treating *H. pylori* infection is daunting and might dissuade some physicians and the government from aggressively managing the infection. However, when one considers the problem one patient at a time, the issue becomes much simpler.

H. pylori diagnosis

The first step in managing *H. pylori* infections is to establish the diagnosis. Physicians in India, as in many

developing countries, face issues of availability and cost to establish the diagnosis of *H. pylori* infection. Worldwide, non invasive tests for active infection are preferred (*e.g.*, urea breath test or stool antigen test) over tests that require endoscopy. Western versions of these tests are relatively expensive but all have been used at one time or another in India. The ^{14}C-urea breath test (UBT) is probably the least expensive. In China, it is available clinically for approximately ₹ 26 per test (DY Graham, personal communication). Endoscopy is available at tertiary care centers but can cost up to ₹150 at a public hospital and between ₹ 450 and 3000 at private clinics[30]. The advantage of endoscopy is that symptomatic patients can be evaluated for mucosal disease. Endoscopy also allows one to take biopsy specimens that can be examined by histology, rapid urease testing, brush cytology, or even culture. Rapid urease tests can be made very cheaply by any hospital laboratory and are reasonably accurate[30,31]. Saksena *et al*[32] showed that the rapid urease test (RUT) and brush cytology had the highest degree of agreement whereas histology was the most specific diagnostic test. The current gold standard to diagnose *H. pylori* infection invasively is two positive tests, which in India could be the combination of the rapid urease test and brush cytology[31,32]. Importantly, the endoscope, the biopsy forceps, and other parts of the system (*e.g.*, water bottles, tubes, rubber ports, *etc.*) can easily become contaminated with *H. pylori*, therefore, it is critical that high-level disinfection be done of all endoscopic equipment and any reusable devices to prevent the iatrogenic spread of the infection or for iatrogenic reinfection post *H. pylori* eradication. The minimally invasive oral brush culture method would seem to be ideal for obtaining culture specimens for susceptibility testing in India[33].

If endoscopy is not available, for symptomatic patients, barium contrast imaging can be used to detect peptic ulcer disease followed by a non-invasive test to confirm *H. pylori* infection. Serologic testing for *H. pylori* antibodies has greater than 80 per cent sensitivity and greater than 90 per cent specificity and is widely available but can cost between ₹200 to 300[30]. Serologic testing is not recommended as the single diagnostic test in asymptomatic patients as it can remain positive for decades after successful *H. pylori* therapy and gives a false positive test result. However, it can be one of the two tests to confirm *H. pylori* infection or combined with a high pretest probability condition such as a duodenal ulcer to confirm the diagnosis.

Choosing the treatment regimen – the effect of antibiotic resistance

Treatment logically follows diagnosis. The goal is to choose a regimen that will reliably produce a 90 per cent or preferably >95 per cent treatment success[2,34,35]. Recommendations from consensus statements should be ignored unless the antibiotic combinations have been proven to be effective locally. Bacterial resistance is the most common cause of treatment failure with what would otherwise be an effective regimen. Resistance is an evolving process such that antibiotic susceptibility and local treatment success rates must be monitored to update treatment selections. Because of the rapid development of resistance, it is recommended that the outcome of every treatment be confirmed with a non invasive test to confirm cure and provide an early warning of changes in local patterns of resistance.

Different antimicrobial agents have been used to treat *H. pylori* infection. Most successful regimens consist of an anti-secretory agent, most often a proton pump inhibitor (PPI) and two or three antimicrobial agents[2,35]. Successful treatment requires consideration of a number of factors (Box 1) including drug, dose, duration, and frequency of drug administration, formulation, and whether the drugs are taken fasting or with meals[37]. These factors are all largely under control of the prescribing physician. If one knows the local resistance rates to the different antibiotics one can generally choose a regimen that will reliably provide at least 90 per cent treatment success. As far as treatment is concerned, it is important to stop considering *H.*

Box 1. Some factors known to influence outcome in *H. pylori* treatment studies

Treatment-specific factors
Manufacturer of the drugs, quality of the formulation
Doses, duration, frequency of drug administration, formulation
Relation of drug administration and meals
Type and dose of adjuvant therapies
Study-specific factors
Methods to detect the infection and to confirm eradication
Prevalence of antimicrobial resistance
Patient-specific factors
Compliance
Cost
Side effects
Genetic polymorphisms that alter study drug metabolism

Source: Ref 36, reprinted with permission

pylori as a "gastroenterology problem" (*i.e.*, in the same light as we might consider gastroesophageal reflux, constipation, or functional bowel disease) and instead consider it as a common bacterial infectious disease more akin to urinary tract infection or pneumonia[38]. Most gastrointestinal diseases are not curable and have a considerable placebo response. In contrast, most common bacterial infectious diseases can be cured and with *H. pylori* there is no placebo response. The lessons learned regarding evaluation of common infections are also applicable to *H. pylori* (*i.e.*, one should expect to cure them all). In addition, the reason for treatment failure should never be a mystery but rather is typically related to resistance or a poor choice of drugs, durations, *etc*.

Easy access to antibiotics contributes to overuse. In India, antibiotics can be obtained without a prescription which leads to overuse or misuse. Worldwide, antibiotics are frequently misprescribed or dispensed incorrectly due to lack of appropriate knowledge, desire to meet patient demands, mistrust in or delayed laboratory results and for economic incentives[39]. Metronidazole is inexpensive, available over the counter and widely used as an anti-diarrhoeal agent and for functional bowel disease. As such, there is generally a high prevalence of metronidazole resistance in India and in other tropical and sub-tropical developing countries[40]. If one were to start with a blank slate, one would probably start by testing locally obtained strains for antimicrobial resistance and use these data to select initial regimens. There are however, data available regarding antimicrobial resistance in India (Tables I & II), and these data suggest that resistance is both common and widespread but with considerable regional variation. Are these data accurate and valuable? To be useful, one would like to know whether the patients tested represented treatment naive patients or *H. pylori* treatment failures, whether they had received the antibiotic in question in the past, their age and socio-economic status and presentation. Accuracy can be assessed in terms of the methods used, whether known susceptible and resistant controls were included and how the results correlated with the results of treatment. In general, the E-test is more difficult to master than agar dilution. The laboratories should present data regarding their methods especially when the results are unexpected (*e.g.*, high levels of amoxicillin resistance) and provide confirmatory testing. The E-test tends to overestimate the prevalence of metronidazole resistance but in experienced laboratories provides accurate results for clarithromycin and amoxicillin resistance[50-52].

Based on the available data regarding antimicrobial resistance, one would expect regimens using clarithromycin or metronidazole to provide unacceptably low eradication rates (Table III). As noted earlier, when examining the results of a clinical trial it is important to take note of the drugs, doses and durations. The report by Bhatia *et al*[47] tested appropriate doses of proton pump inhibitor (PPI), amoxicillin, tinidazole or clarithromycin for 14 days in a sufficient sample of patients (*i.e.*, approximately 70 each) and used three tests

Table I. Regional *H. pylori in vitro* antibiotic resistance in India

Antibiotic	Study	Number patients	Location	Resistance rate (%)
Clarithromycin	Thyagarajan *et al*[41]	259	Multi-center	45
	Mhaskar *et al*[42]	15	Mumbai	91
	Abraham *et al*[43]	7	Mumbai	100
Amoxicillin	Thyagarajan *et al*[40]	259	Multi-center	33
	Devarbhavi *et al*[4]	n/a	n/a	40
	Mhaskar *et al*[42]	15	Mumbai	73
	Krishna *et al*[44]	n/a	n/a	6
Tetracycline	Datta *et al*[45]	67	Kolkata	8
	Mhaskar *et al*[42]	1	Mumbai	27
	Sharma *et al*[46]	5	n/a	10
Levofloxacin	Mhaskar *et al*[42]	15	Mumbai	0

n/a, not available

Table II. Regional *H. pylori in vitro* metronidazole resistance in India

Study	Number isolates	Location	Resistance rate (%)
Datta *et al*[45]	67	Kolkata	85
Bhatia *et al*[47]	31	North India	42
Thyagarajan *et al*[41]	259	Multi-center	78
Mukhopadhyay *et al*[48]	n/a	Kolkata	90
Devarbhavi *et al*[4] Krishna *et al*[44]	n/a	Mumbai & Hyderabad	16
Abraham *et al*[43]	60	Mumbai & Lucknow	70
Mhasker *et al*[42]	15	Mumbai	100
Sharma *et al*[46]	n/a	Lucknow	66
Banatvala *et al*[49]	30	Migrant study in UK (Bangladeshis)	90

to confirm cure to provide reliable data. The treatment success with clarithromycin-containing triple therapy was 42 and 65 per cent for tinidazole-containing triple therapy thus confirming the hypothesis that in Mumbai, legacy triple therapy provides unacceptably low treatment results. By contrast, in New Delhi the same regimen provided 80 per cent success after 14 days and 91 per cent after 21 days[55]. However, in this study the sample sizes were too small to provide a meaningful comparison between the 14 and 21 day groups. Without having concomitant susceptibility data, it is difficulty to suggest the mechanisms responsible for this surprising result. Most of the Indian studies have used less than optimal dosing, duration, or both and thus are not very helpful in deciding what to use and in which situation. The fact that sequential therapy provided 87 per cent treatment success in Puducherry suggests that the local resistance rate for clarithromycin was less than 20 per cent[53].

Which regimens are likely to be effective in India?

The available data from India do not provide the information one requires to prospectively identify a successful treatment regimen. India is ripe for prospective studies of different anti-*H. pylori* therapies. The investigators should follow the recommendations for efficient identification of effective regimens that allows one to expose the minimal number of subjects to a new regimen but at the same time, starts with one's "best shot" in terms of dose, duration, frequency of drug administration, *etc*[2,35,63]. Treatment failures are very difficult to interpret unless one has susceptibility data. Such data do not need to be acquired before the trial but a biopsy or two can be saved frozen at -70C in transport media for subsequent culture and susceptibility testing locally or following shipment to a central laboratory in India or elsewhere.

If it were decided to routinely treat all *H. pylori* infections diagnosed in India, what regimen or regimens would be most likely be successful? Ideally, for an infectious disease, one would have information from clinical trials regarding which regimens were most effective (*e.g.*, reliably provide 90% or greater treatment success) in that population as well as the effect of resistance to the antibiotics used both individually and in combination. The regimens would also have been optimized in terms of dose, drugs, and duration. This has been accomplished, at least partly, for most commonly used regimens in the West (Table IV and Box 2). In general, the results from one location are transferrable to another region provided the patterns of resistance are the same. Clearly in India, the problem of antibiotic resistance differs greatly from that in developed western countries. In addition, the pattern of resistance appears to vary widely and data regarding resistance in most areas are scant and not necessarily reflective of that population. In addition, although several trials have been done in India, most were small, rarely evaluated what are now known to be the optimal formulations, and often used lower than optimal doses and durations. An India-wide systematic approach is needed to identify the best regimen in general and specifically for each area. These results would be enhanced by simultaneous collection of susceptibility data and effectiveness from different populations throughout India.

Until accurate treatment data combined with susceptibility testing data are available, one must rely on

Table III. *H. pylori* treatment regimens in India

Study	Number patients	Location	Duration	Treatment regimen	Eradication rate (%)	Test of eradication
Valooran *et al*[53]	73	Pondicherry	10 days	Omeprazole Clarithromycin Amoxicillin	81 per protocol	RUT Histology
			Sequential 5 days	Omeprazole Amoxicillin	87 per protocol	
			Followed by 5 days	Omeprazole Amoxicillin Clarithromycin		
Ahuja *et al*[54]	28 Previous treatment failures	New Delhi	10 days	Rifampicin 450 mg q.d. Tetracycline 1000 mg b.i.d. Esomeprazole 40 mg b.i.d.	32 Intention to treat 33 Per protocol*	RUT UBT Histology
Chaudhary *et al*[55]	21	New Delhi	7 days	Lansoprazole 30 mg b.i.d. Amoxicillin 1000 mg b.i.d. Tinidazole 500 mg b.i.d.	48	RUT UBT
	20		14 days		80	
	23		21 days		91*	
Bhatia *et al*[47]	70	Mumbai	14 days	Lansoprazole 30 mg b.i.d. Amoxicillin 1000 mg b.i.d. Tinidazole 500 mg b.i.d.	42 Per protocol	RUT UBT Histology
	76			Lansoprazole 30 mg b.i.d. Amoxicillin 1000 mg b.i.d. Clarithromycin 500 mg b.i.d.	65 Per protocol*	
Pai *et al*[56]	35	Manipal	10 days Lansoprazole 30 mg bid with:	Amoxicillin 500 mg q.i.d. Clarithromycin 500 mg b.i.d.	83 Intention to treat 88 Per protocol	In-house RUT Histology
	33			*Dicitrato bismuthate 120 mg q.i.d. Metronidazole 400 mg t.i.d. Tetracycline 500 mg q.i.d.*	73 Intention to treat 86 Per protocol	
Kumar *et al*[57]	32	New Delhi	7 days	Lansoprazole 30 mg q.d. Clarithromycin 500 mg b.i.d. Secnidazole 2000 mg days 1,4,7	75	RUT UBT

Contd...

Study	Number patients	Location	Duration	Treatment regimen	Eradication rate (%)	Test of eradication
	32			Lansoprazole 30 mg q.d. Amoxicillin 1000 mg b.i.d. Bismuth subcitrate 240 mg b.i.d. Secnidazole 2000 mg on days 1,4,7	75	
Bhasin *et al*[58]	22	Chandigargh	7 days	Lansoprazole 30 mg q.d. Clarithromycin 250 mg b.i.d. Amoxicillin 500 mg t.i.d.	54	RUT Histology
	24		14 days	Lansoprazole 30 mg q.d. Clarithromycin 250 mg b.i.d. Amoxicillin 500 mg t.i.d.	96*	
Bhasin *et al*[59]	22	Chandigargh	14 days	Omeprazole 40 mg q.d. *Clarithromycin 250 mg b.i.d.*	68	RUT Histology
	20		14 days	Omeprazole 40 mg q.d. *Clarithromycin 250 mg b.i.d. Amoxicillin 500 mg t.i.d.*	70	
	22		14 days	*Bismuth subcitrate 120 mg q.i.d. Amoxicillin 500 mg t.i.d. Metronidazole 400 mg t.i.d.*	59	
Ahuja *et al*[60]	21	New Delhi	14 days	Lansoprazole 30 mg q.d. Amoxicillin 500 mg q.i.d. Secnidazole 2000 mg q.o.d.	86 Intention to treat	In-house RUT UBT
	21		14 days	Lansoprazole 30 mg q.d. Pefloxacin 400 mg q.d. Secnidazole 2000 mg q.o.d.	71 Intention to treat	
	18		7 days	Lansoprazole 30 mg q.d. Clarithromycin 500 mg b.i.d. Secnidazole | 2000 mg q.o.d.	83 Intention to treat	

Contd...

Study	Number patients	Location	Duration	Treatment regimen	Eradication rate (%)	Test of eradication
Gupta *et al*[61]	50 total	New Delhi	14 days	Lansoprazole Norfloxacin	77	n/a
	n/a		14 days	Omeprazole Norfloxacin	64*	
Dayal *et al*[62]	46	Patna	Days 1-30	Bismuth subcitrate 240 mg b.i.d.		RUT Histology
			Days 1-14	*Metronidazole 400 mg t.i.d. Tetracycline 500 mg q.i.d.*	67	
Sawant *et al*[63]	15	Mumbai	7 days	*PPI q.d. Clarithromycin 250 mg b.i.d. Tetracycline 500 mg b.i.d.*	87	RUT Histology or Cytology
	15		14 days	PPI q.d. Amoxicillin 500 mg q.i.d. *Tetracycline 500 mg b.i.d.*	53	

*$P<0.05$; italics are used for antibiotics given at possibly lower than optimal doses
RUT, rapid urease test; UBT, urea breath test; b.i.d., twice daily; t.i.d., thrice daily; q.d., every day; q.i.d., four times a day; q.o.d., every other day

first principles, (*e.g.*, cannot overcome clarithromycin resistance or fluoroquinolone resistance by increasing either the dose or duration of therapy and these antibiotics are best avoided in regions where resistance is known to be high either from direct assessment or from a history of poor treatment success). In contrast, metronidazole/tinidazole resistance can be partly or largely overcome by using full doses (1,500 to 1,600 mg) and a 14 days of therapy. The quadruple therapy consisting of tetracycline, metronidazole, bismuth, and a PPI (Box 2) has been tested directly in metronidazole resistance and has generally had a success rate of 90 per cent or greater provided that therapy is at least 10 and preferably 14 days[66-69]. Bismuth quadruple therapy would be one of our first choices for testing. The reports of tetracycline resistance in India are troubling but the intragastric doses are very high and the effect of different levels of tetracycline resistance on outcome has not been assessed directly. An alternate would be the same combination but substituting furazolidone (or possibly secnidazole or even clarithromycin) for the metronidazole. The optimal dose of furazolidone is unknown; we use 100 mg t.i.d. with meals. A few caveats are necessary when using furazolidone. The drug is an monoamine oxidase inhibitor and thus interacts with many other drugs and foods (*e.g.*, we provide patients with an information sheet that cautions against aged cheese, sausage including bologna, salami and pepperoni, lima beans, lentils, snow peas, and soybeans, canned figs and raisins, beer, ale and wine, licorice, soy sauce and any food product that is made with soy sauce, monamine oxidase inhibitors, phenylpropanolamine, ephedrine, and phenylephrine). A widely read letter to the editor stated that furazolidone had been removed from the US market because it was a proven carcinogen[70]. That information is erroneous; the author mixed animal food supplement regulations with human medicine. Furazolidone was originally sold in the U.S. by Roberts Pharmaceuticals which was purchased by Shire Pharmaceuticals which because there was almost no commercial market for the drug, chose not to continue to market the drug and notified the Food and Drug Administration (FDA) that they would stop marketing it. The FDA responded that they would "publish a notice in the Federal Register stating that you have voluntarily requested withdrawal of approval

Table IV. Antimicrobials used for *H. pylori* eradication therapy

Drug	Optimal doses
Amoxicillin	2 g daily
Bismuth compounds	240 mg per dose for subcitrate
Clarithromycin (macrolides)	1 g daily
Fluoroquinolones	Once daily is sufficient
Furazolidone	Unknown vs. 100 mg t.i.d.
Metronidazole/tinidazole	1 g daily for b.i.d. therapy 1.5 g daily for bismuth quadruple therapy
Nitazoxanide	Unknown
Rifabutin	Unknown
Secnidazole	Unknown
Tetracycline HCl	2 g daily for bismuth quadruple therapy

Source: Ref 65

of these applications because you have stopped marketing the drug products under the NDA". That notice was subsequently published (Federal Register / Vol. 70, No. 42 / Friday, March 4, 2005 / Notices, pp 11652). The letter to the editor described furazolidone as a carcinogen although it is listed by the IARC as a Group 3 carcinogen which is defined as "unclassifiable as to carcinogenicity in humans"[70].

Clarithromycin-containing triple therapies are very effective regimens provided the appropriate doses and duration are used and local resistance to clarithromycin is low. The success rate with legacy triple therapy consisting of a twice a day PPI plus amoxicillin and clarithromycin or clarithromycin and metronidazole falls below 90 per cent when the level of clarithromycin resistance is 7 to 10 per cent[38]. Sequential therapy is an effective alternative until clarithromycin resistance exceeds 20 per cent and metronidazole resistance exceeds 40 per cent and then treatment success falls to unacceptable levels[71]. As such triple therapy should be avoided unless it were proven to be locally effective; there are likely few places in India where sequential therapy would provide 90 per cent or greater success. If one were to try a 4 drug clarithromycin containing regimen we suggest trying hybrid therapy (Box 2) as it has the best chance of being successful[72]. Alternatively, one could use bismuth-clarithromycin quadruple therapy but this would also need to be optimized for India (Box 2).

Development of India-specific regimens

The old concept of trial and error that was the norm for early *H. pylori* therapies has passed as it has become recognized that the same approaches used for other common infectious disease is likely to provide better results[36]. We now recognize that treatment results are predictable provided we know the pattern of resistance in a community. This allows us to quickly identify and optimize, (or reject) potential regimens, exposing the fewest patients to ineffective therapy. Simply trying some combination in an arbitrary number of subjects is no longer considered rational or ethical. For example,

Box 2. Recommended anti-*H. pylori* therapy

Bismuth-containing regimen

Bismuth-metronidazole quadruple therapy: Bismuth subsalicylate or subcitrate 2 tabs q.i.d,, tetracycline HCl 500 mg q.i.d., metronidazole or tinidazole 500 mg, t.i.d. or 400 mg q.i.d. (with meals and bedtime) plus a PPI b.i.d. *Effective in the presence of metronidazole resistance.*

Bismuth-furazolidone quadruple therapy: Bismuth subsalicylate or subcitrate 2 tablets q.i.d, tetracycline HCl 500 mg q.i.d.(with meals and bedtime), furazolidone 100 mg, t.i.d. (with meals) and a PPI b.i.d. for 10 to 14 days. *Effective in the presence of multidrug resistance but with considerable incidence of side effects.*

Bismuth clarithromycin quadruple therapy: Bismuth subsalicylate or subcitrate 2 tablets q.i.d,, tetracycline HCl 500 mg q.i.d., clarithromycin 500 mg, b.i.d, plus a PPI b.i.d. *We have no experience with this regimen in the face of clarithromycin resistance but a recent paper from China suggested reasonable effectiveness*[64].

Clarithromycin-containing 4 drug regimens

Sequential therapy: Amoxicillin 1 g plus a PPI b.i.d. for 5 days, then add clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d, to complete 10 days. *Not likely to be highly successful well evaluated in areas with high combined metronidazole and clarithromycin resistance.*

Concomitant therapy: Amoxicillin 1 g, clarithromycin 500 mg, tinidazole or metronidazole 500 mg, a PPI all given b.i.d. for 10 to 14 days. *Not well evaluated in areas with high combined metronidazole and clarithromycin resistance but not likely to be highly successful*.

Sequential-concomitant hybrid therapy: Amoxicillin 1 g plus a PPI b.i.d. for 7 days, then amoxicillin 1 g b.i.d., plus clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d for 7 days to complete 14 days. *Never evaluated in areas with high combined metronidazole and clarithromycin.*

Experimental therapy

High dose PPI dual therapy: Examples: omeprazole 40 mg or lansoprazole 30 mg plus 500 mg amoxicillin q.i.d. at 7:00, 12:30, 19:00, 23:00 p.m. for 14 days. *Used successfully in Japan*[65].

secnidazole has been used with some success in India although attempts to optimize its use and identify its effectiveness in the presence of metronidazole resistance are lacking. India has been on the forefront of suggesting new antibiotic formulations that differ in their intragastric time[73,74]. However, this idea has not been advanced further with *in vivo* testing.

Recurrence of *H. pylori* after treatment

A high rate of reinfection after eradication in developing countries would undermine attempts to eradicate the infection in individuals, families, villages, or larger groups of individuals. Recurrence of infection following what appears to have been successful therapy is classified as either recrudescence, a form of failed therapy in which the same *H. pylori* strain is still present, or as reinfection when a different strain is present[75]. These definitions are general as recrudescence can actually be reinfection from a common source and reinfection from outgrowth of a minor population of a mixed infection. Recurrence, either reinfection or recrudescence, is more common following low treatment success regimens suggesting that most cases represent recrudescence. Recurrence within 12 months of treatment in developed countries is generally due to recrudescence[76]. Since sanitation in developed countries is generally good there and the prevalence of *H. pylori* is low, particularly in children, re-exposure is less problematic. However, in developing countries sanitation is often suboptimal and the presence of the infection is almost universal thus the potential for reinfection is high. Whether this is an actual problem in India is unclear (Table V) and is an excellent area for research. Studies in India in which individuals or families are followed prospectively using non-invasive tests after successful eradication are needed. Molecular characterization of the infecting strains such as RFLP (restriction fragment length polymorphism) checked before treatment and following recurrence would be needed to help unravel this problem and discover whether recurrence following eradication is a problem that must be addressed or mostly a theoretically concern[76,81,82]. Routine endoscopy for surveillance should probably be avoided to reduce the possibility of iatrogenic reinfection from confusing the picture. One would imagine that the population at highest risk would be one living in poverty in relatively unsanitary conditions without access to potable water. Data over a longer interval (*e.g.*, 5 year) regarding reinfection from the Indian subcontinent are needed in populations that eradication was definitely confirmed using 2 or 3 tests or a single test (*e.g.* urea breath test) on at least 2 occasions.

Recommendations for the future

India is an ideal place for investigation of new ideas in a systematic and organized way as the infrastructure is present, the pharmaceutical industry is among the most innovative, and the medical expertise highly regarded and up to date. Questions that might

Table V. Recurrence of *H. pylori* infection studies from India and Bangladeshi

Study & location	Number patients	Eradication rate (%)	Recurrence rate (%)	Time to recurrence	Test of recurrence
Ahmad *et al*[77] Bangladesh	47	n/a	5	72 months	UBT EGD
Hildebrand *et al*[78] Bangladesh	105	92	14	Within 3 months	UBT "Biopsy based"
			13	At 3 months and 18 months post treatment	
Bapat *et al*[79] Mumbai, India	64	89 after 2 wk of quadruple therapy 80 after 1 wk of salvage therapy 80	2	12 month median follow up Range 9-15 months	RUT Histology Antral biopsy
Nanivadekar *et al*[80] Mumbai, India	66	n/a	HP and PUD: 63 PUD: 10*	3 months to 3 years 91 exams total	n/a

*$P<0.05$; n/a, not available
HP, histopathology; PUD, peptic ulcer disease; UBT, urea breath test; EGD, oesophago gastrodudenoscopy; RUT, rapid urease test

be addressed include what is the recurrence rate of *H. pylori* infection after successful eradication. If the recurrence rate is high, what factors are responsible and how can it be reduced (*e.g.*, the source of reinfection and whether it can be managed) and whether eradication of the infection from entire families or villages would eliminate recurrence. The high level of antimicrobial resistance allows direct study of agents in the presence of different patterns of resistance. It is imperative that susceptibility be assessed accurately and, if required laboratory personnel or individual technicians can be trained in the details of susceptibility testing for *H. pylori* and in designing treatment trials to investigate current and innovative treatment regimens. India should be leading the way in the research of treatment of *H. pylori* infections. Ultimately, eradication of *H. pylori* from India and other developing countries may need to await development of an effective vaccine[83].

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