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ASSESSMENT OF PATTERN OF ANTIMICROBIAL RESISTANCE OF HELICOBACTER PYLORI IN PATIENTS OF DYSPEPSIA OF RURAL AREA

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ABSTRACT: BACKGROUND: Helicobacter Pylori is a gastric pathogen that chronically infects more than half of the world's population. Unless treated, colonization usually persists lifelong. H. pylori infection represents a key factor in the etiology of various gastrointestinal diseases, ranging from chronic active gastritis without clinical symptoms to peptic ulceration, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Helicobacter pylori eradication rate varies in different parts of the world. This may be related to the regional difference in anti-microbial resistance that affects the outcome of therapy, genetic difference in the metabolism of the proton pump inhibitor, which can also alter the availability of anti-microbial in the stomach. The pattern of antimicrobial resistant of Helicobacter pylori has not been tested in this part of central India. In present study we have assessed the pattern of anti-microbial resistance of Helicobacter Pylori in patients of dyspepsia attending medicine opd, Department of Medicine, Dr. BRAM Hospital, Raipur (Chhattisgarh), India. **METHODS:** The present study was conducted in the Department of Medicine, Pt. J. N. M. Medical College, and Dr. BRAM Hospital Raipur (C.G.) 60 patients attending medicine opd were subjected to upper gastrointestinal endoscopy. Multiple biopsy specimens taken from the gastric antrum. Rapid urease test were done. The biopsy specimen was inoculated in to culture media. The strains were subjected to antibiotic sensitivity test by disk diffusion method for metronidazole, tinidazole, Ornidazole, Clarithromycin, amoxicillin, tetracycline, furazolidone, ofloxacin and ciprofloxacin. **RESULT:** The antibiotic resistance of H. Pylori in culture positive cases in our study showed 84.6%o of cases were resistant to Metronidazole, 38.5% to Tinidazole, 7.6%o to Ornidazole, 32.8% to Amoxicillin, 3.8% to Tetracycline, 19.2% to Clarithromycin, 11.5% to furazolidone, and 3.8% to Ciprofloxacin.

INTRODUCTION: Helicobacter pylori is a gastric pathogen that chronically infects more than half of the world's population, with a prevalence ranging from 25% in developed to more than 90% of in developing areas.[1] Infection with H. Pylori is associated with chronic gastritis, peptic ulcer and MALT lymphoma and adenocarcinoma of stomach. The reason for such a clinically diverse outcome of infection remains uncertain, but may include host and environmental factors as well as differences in the prevalence or expression of bacterial virulence factors.[1]

Helicobacter pylori eradication is successful in 80% to 90% of the cases. This means up to 10-20% of the eradication therapy failed. The commonest reasons for failed eradication therapy include bacterial resistance to anti-microbial and patient non-compliance to treatment. Other factors are smoking, alcohol, inadequate dose of acid suppressants and inadequate doses of antibiotics.

Helicobacter pylori eradication rate varies in different parts of the world. This may be related to the regional difference in anti-microbial resistance that affects the outcome of therapy, genetic difference in the metabolism of the proton pump inhibitor, which can also alter the availability of

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anti-microbial in the stomach. Some studies also suggested that the degree of gastritis and the nature of the underlying disease may affect the outcome of therapy but this is controversial.

In present study, our aim is to assess the pattern of antimicrobial resistance of Helicobacter pylori in patients of Dyspepsia attending medicine opd, Department of Medicine, DRBRAM Hospital, Raipur, (Chhattisgarh).

AIMS AND OBJECTIVES: To assess the pattern of antimicrobial resistance of helicobacter pylori in patients of Dyspepsia attending medicine opd, Department of Medicine, DRBRAM Hospital, Raipur (Chhattisgarh, India)

MATERIAL AND METHODS: 60 Cases were taken among patients who had attended the medicine opd, Department of Medicine, DRBRAM Hospital, Raipur (Chhattisgarh, India).

Inclusion Criteria:
1. Age more than 15 years and less than 50 years.
2. Patients with dyspepsia of >1 month duration.
3. Patients with dyspepsia not responding to antacid, PPI and H2 blockers (But have not taken PPI and H2 blockers within last two weeks).

Exclusion Criteria:
1. Patients more than 50yrs of age with new onset dyspepsia of short duration with alarming signs e.g. weight loss, melena with anemia, dysphagia, recurrent vomiting.
2. Patients who have already received anti helicobacter pylori treatment.
3. Patients with severe cardiopulmonary co-morbid illness.
4. Patients with diabetes, renal disease, liver disease.
5. Patients with history of use of Steroid, NSAIDS and who had taken PPI or H2 Blocker within two weeks.
6. Pregnant and lactating females.

All above patients were subjected to upper gastrointestinal endoscopy by Olympus video endoscope. Multiple biopsy specimens taken from the gastric antrum. Rapid urease test were done immediately with biopsy specimen. The biopsy specimen was inoculated in to media containing urea with a pH sensitive dye at room temperature. The colour change was noted after every 1/2hours for first 2hours and then at 24hours. A positive reaction showed colour change of solution from yellowish orange to pink.

Another fresh biopsy specimen were transported for culture in isotonic saline within 4 hours duration. The fresh biopsy specimen was homogenized and inoculated directly to Campylobacter agar base and park and Sander's selective supplement II base and streaked for isolation.[2] It is a blood agar base II supplemented with vancomycin, polymyxin B, cephalothin, Amphotericin B and trimethoprim to inhibit commensal bacteria and fungi.[3]

The plates were incubated at 37^0C in a gas pak jar to create microaerophilic condition incubation was carried out for 3-5 days. The colonies of H. Pylori appear as non-hemolytic, flat, gray with irregular or raised or round edge and mucoid appearance.[4]

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The strains were subjected to antibiotic sensitivity test by disk diffusion method for metronidazole, tinidazole, ornidazole, clarithromycin, amoxicillin, tetracycline, furazolidone, ofloxacin and ciprofloxacin.

OBSERVATIONS: 60 patients with history of dyspepsia attending medicine opd, Department of Medicine, Dr. Bram Hospital, Raipur were evaluated.

1. Most patient (56.6%) belongs to age group 35-50 years, 26.6% patients belongs to age group 15-25 years, 16.6% patients belongs to age group 26-35year.
2. 63.3% patients had history of Pain in upper abdomen, 20% patients had history of Fullness after meal, 16.6% patients had Retrosternal burning pain, 30% patients had nausea, 21.6% patients had vomiting, 15% patients had Water brash 6.6% patients had melena, 10% had Hemetemesis and 26.6% had Anorexia.
3. There were 39(78.3%) male and 11(21.7%) females' patients, 40% patients had history of smoking, 13.3% patients had history alcoholism, 40% patients had history of spicy food intake, most of patients used untreated water (90%) and most patients belong to low socio-economical group (90%).
4. The previous treatment taken by patients included antacid 42(70%), H2 blockers 24(40%) and proton pump inhibitors 21(35%) (Not on PPI and H2 blockers since last two weeks).

Grade	No. of patients	Percentage
Grade I	9	15%
Grade II	28	46.7%
Grade III	18	30%
Grade IV	5	8.3%
Grade V	0	0%
Table 1: Symptoms Scale Assessment Of Dyspeptic Patients (Likert Scale)		

Grade	Severity	Frequency	Typical duration
I	None	<2 times/week	<10 minutes.
II	Mild	>3 times/week (not daily)	10-30 minutes
III	Moderate	Daily, Intermittent	>30 minutes
IV	Severe	Daily, almost continuous	Almost continuous
V	Very severe	Daily, almost Continuous	Almost continuous
Likert Scale			

5. In Likert Scale, 28(46.7%) patients had grade II symptoms, 18(30%) patients had grade III symptoms, 9(15%) patients had grade I symptoms, 5(8.3%) patients had grade IV symptoms.
6. 38 cases out of 60 dyspeptic patients gave positive rapid urease test with pyloric antrum biopsy specimens 89.4% cases by RUT were positive within ½ hour, 5.2% took up to 1 hour and remaining 5.2% case become positive within 1-1½hours, none of case took more than 1½ hours in 38 positive cases. This indicates that majority of patients were heavily infected with Helicobacter Pylori (>10^6 bacteria/biopsy tissue).

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Sl. No.	Endoscopic Finding	No. of Patients	Percentage	Positivity by RUT	Percentage
1	Antral gastritis	25	41.7%	22	88%
2	Duodenitis	13	21.6%	10	76.9%
3	Duodenal ulcer	7	11.6%	7	100%
4	Gastric ulcer	4	6.6%	3	75%
5	Normal appearance	28	46.6%	9	32.1%
Table 2: Relation of Endoscopic Finding and Helicobacter Pylori Positivity by Rapid Urease Test (RUT) In All Cases of Dyspepsia					

7. 100% duodenal ulcer and 75% of gastric ulcer patients, 88% of gastritis and 76.9% of Duodenitis patients were positive for Helicobacter pylori and about 32.1%) with normal UGI Endoscopy finding dyspeptic patients were RUT positive for H. Pylori.

Sl. No.	Endoscopic finding	No. of Cases	Culture Positive	Percentage
1.	Antral Gastritis	25	17	68%
2.	Duodenitis	13	8	61.5%
3.	Duodenal ulcer	7	5	71.4%
4.	Gastric ulcer	4	2	50%
5.	Normal appearance	28	8	28.6%
Table 3: Relation of Endoscopic Finding and Helicobacter Pylori Positivity by Culture in All Cases				

8. In our study 68% patients with Antral gastritis, 61.5% patients with Duodenitis, 71.4% patients with duodenal ulcer, 50% patients with gastric ulcer were positive by culture method, 28.6% of normal UGI Endoscopy finding dyspeptic patients were culture positive for H. Pylori.

SL. No	Drugs	No. of cases	Percentage
1.	Metronidazole	22	(84.6%).
2.	Tinidazole	10	(38.5%)
3.	Ornidazole	2	(7.6%)
4.	Amoxicillin	10	(38.4%)
5.	Tetracycline	1	(3.8%)
6.	Clarithromycin	5	(19.2%)
7.	Furazolidone	3	(11.5%)
8.	Ciprofloxacin	1	(3.8%)
Table 4: Resistance of Helicobacter Pylori to Antibiotics in Culture Positive Cases			

9. The antibiotic resistance of H. Pylori in culture positive cases in our study showed 84.6% of cases were resistant to Metronidazole, 38.5% to Tinidazole, 7.6% to Ornidazole, 32.8% to Amoxicillin, 3.8% to Tetracycline, 19.2% to Clarithromycin, 11.5% to Furazolidone, and 3.8% to Ciprofloxacin.

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DISCUSSION: Helicobacter pylori is now considered to play an important role in the etiopathogenesis of peptic ulcer, chronic gastritis, gastric malignancies like MALT lymphoma and adenocarcinoma of stomach. Although most human who are infected will never develops symptoms.

The treatment of Helicobacter pylori is difficult because of rapid development of resistance to antimicrobial agents especially in patients from developing countries like India.

The pattern of antimicrobial resistant of Helicobacter pylori has not been tested in this part of central India. In present study we have assessed the pattern of anti-microbial resistance of Helicobacter Pylori in patients of dyspepsia.

The majority (56.6%) patients belonged to the age group 35-50years. The male and female ratio was 47:13. The incidence of H. Pylori infection was found maximum in the age group 35-50 years. This was contrast to incidence of H. Pylori infection is western countries like USA, where most of patients were found to be above 60yrs (Graham Dy et al.)[5] The predominance of younger age group is our study group might be due to the fact that the patient belonged to low socio economic status with poor hygienic condition in whom H. Pylori infection is acquired at an early age as compared to Western countries (Gill HH et al.)[6] studies 526 patients of dyspepsia at Bombay and found that maximum prevalence of H. Pylori infection was in age group of second to fourth decade.

In our study we found that most common symptom in H. Pylori infected patients was Pain in upper abdomen 63.3%, 20% patients had history of Fullness after meal, 30% patients had nausea, 21.6% patients had vomiting, 15% patients had Water brash,6% patients had melena,10% had Hemetemesis and 26.6% had Anorexia.

Most patients belonged to low socio-economical group and they were consuming unsafe water. As per medical journal of Allina Vol. 6, No. 3 summer 1997. The H. Pylori survive in water sources for at least 48 hours, while in Buckley O Dublen et al. from Ireland reported that the organism could remain metabolically active in water for at least a week and cocci forms have found to present for at least a year in river. 40% patients had history of spicy food intake.

In our study 70% patients had taken antacid as treatment during various times for relief of their symptoms, 40% had taken H2 blockers and 35% proton pump inhibitors (Not on PPI and H2 blockers since last two weeks). This indicate that a large number of patients had taken various drugs for symptomatic relief without much benefit. This substantiates the fact that if simple anti-ulcer drugs are taken symptomatic relief will be followed by recurrence of dyspepsia at a later time (David A. Peura 1997).[7]

In our study, 38 cases out of 60 dyspeptic patients gave positive rapid urease test with pyloric antrum biopsy specimens 89.4%) cases by RUT were positive within ½ hour, 5.2% took up to 1 hour and remaining 5.2% case become positive within 1-1½ hours, none of case took more than 1½ hours in 38 positive cases. This indicates that majority of patients were heavily infected with Helicobacter Pylori (>10^6 bacteria/biopsy tissue)

In our study, out of total 60 cases antral gastritis present in 25 patients (41.7%), duodenitis in 13 patients (21.6%), duodenal ulcer in 7 patients 11.6%), gastric ulcer in 4 patients (6,6%). In this group 90.6%(29/32) patients were positive rapid urease test. 100% duodenal ulcer and 75% of gastric ulcer patients, 88% of gastritis and 76.9% of duodenitis patients were positive for Helicobacter pylori by RUT and about 32.1% with normal UGI Endoscopy finding dyspeptic patients were RUT positive for H. Pylori. Vijaya VA Myosorekar et al. studied 355 patients and found that H. Pylori was associated in 45% of cases of gastritis, 54% cases of duodenitis, 91% cases of duodenal

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ulcer. The reason for the difference in incidence of high H. Pylori infection in our study may point out to higher rate of H. Pylori prevalence in and around Raipur.

Upper GI endoscopy showed normal endoscopic appearance in 46.6% cases, 9 out of their 28 normal endoscopy finding patients were found infected with H.Pylori, so association of H.Pylori was found to be 32.1% in normal UGI endoscope dyspepsia patients, Vijaya VA Myosorekar and Chitralekha et al. studied 355 patietns and found H.Pylori was associated 44%) cases of non-ulcer dyspepsia. Taley TJ et al. suggested H.Pylori in 50% cases of non-ulcer dyspepsia.

The bacterial culture is unquestionably the most specific but it is subjected to sampling errors and may give false negative a results.[16] In our study group biopsy of 18 patients (56.25%) out of 32 endoscopy positive cases grow in culture media out of which 68%) patients with Antral gastritis, 61.5%) patients with duodenitis, 11.4% patients with duodenal ulcer, 50% patients with gastric ulcer were positive by culture method, Which is comparable to 65.8%) by Sivprakash R.Rao[17] The low rate of isolation is possibly due to sub-optimal quality of locally available media, high contamination, delay in processing and difficulty in achieving the required gaseous environment, which is critical for isolation. In non-ulcer dyspepsia group 8 out of 28 biopsy sample (28.6%) were grow in culture media.

The antibiotic resistance of H. Pylori in culture positive cases in our study showed 84.6%) of cases were Resistant to Metronidazole, 38.5%) to Tinidazole, 7.6% to Ornidazole, 32.8% to Amoxicillin, 3.8% to Tetracycline, 19.2% to Clarithromycin, 11.5% to furazolidone and 3.8% to Ciprofloxacin.

The occurrence of Metronidazole-resistant strains may be the consequence of increased consumption of this antibiotic in the community. In this study, the resistance to Metronidazole was observed in 84.6% of strains. Metronidazole has been widely prescribed for other infections such as parasitic or genital infections, and the use or abuse of this inexpensive drug may contribute to the increase in Metronidazole resistance.[8]

Furazolidone has been used as an alternative to overcome Metronidazole resistance. In our study, resistance to furazolidone was 11.5%, higher than rates "detected by others. The reason for the high rate of furazolidone resistance and factors leading to it are still unknown and deserve further investigation.

In a multi-center study from India (Delhi, Chandigarh, Lucknow, Hyderabad and Chennai), 259 isolates of H.Pylori were tested for in vitro susceptibility to antibiotics, of these, 77.9% has resistance to metronidazole, 44.7% had resistance to metronidazole, 44.7% to Clarithromycin and 32.8% to amoxicillin.[9]

In another study of 67 clinical isolates of H.Pylori from Kolkata, 85% were resistant to Metronidazole and 7.5% to Tetracycline, but most were sensitive to Clarithromycin, furazolidone and Amoxicillin.[10]

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Cases Resistant in different studies	In our study (n-26)	SP Thyagarjan Multicentric study[9] (2003) (n-259)	S. Datta Kolkata (2003) (n-62)	Lucknow Capt. RN Mishra[11] (2006) (n-62)	MACH Multi-national study (1999) (n516)	Brazil Mandonca. S[12] (2000) (n-90)	Bangla desh Shamsum Nahar[9] (2004) (n-120)
Drugs							
Metro-nidazone	22 (84.6%)	77.9%	85%	93%	27% (16.42%)	42%	77.5%
Tindazole	10 (38.5%)	-	-	-	-	-	-
Ornidazole	2(7.6%)	-	-	-	-	-	-
Amoxicillin	10 (38.4%)	32.8%	Highly Sensitive	64.1%	Highly Sensitive	29%	6.6%
Tetracycle	1(3.8%)	1-4%	7.5%	28.5%		7%	15%
Clarit-hromycin	5 (19.2%)	44.7%	Highly Sensitive	71.4%	3%	7%	10%
Fura-zolidone	3 (11.5%)	-	Highly Sensitive	-	-	4%	-
Cipro-floxacin	1 (3.8%)	1-4%	-	-	-	-	-
Table 5: Comparison of Resistance of Helicobacter Pylori to Antibiotics in Culture Positive Cases in Our and Others Studies							

Another Indian study of 62 clinical Isolates of H. Pylori from Lucknow, 93% were resistant to Metronidazole, 64.1% for Amoxicillin, 71.4% to Clarithromycin, 28.5% Tetracycline.[11]

Another study from Bangladesh, Antimicrobial susceptibility of 120 Helicobacter pylori isolates to Metronidazole, tetracycline, Clarithromycin, and Amoxicillin was determined, and 77.5, 15, 10, and 6.6% of the isolates, respectively, were resistant.

In MACH 2 study, Culture and susceptibility testing of Helicobacter pylori strains was performed in a large multinational, multicenter randomized clinical trial. Patients with duodenal ulcer disease at 47 centers in six countries (France, Germany, Ireland, Norway, Sweden, and the United Kingdom) were included in the study. Culture was carried out on gastric biopsy samples obtained from 516 patients, Susceptibility testing was performed for clarithromycin and Metronidazole on 485 strains by an agar dilution method and the epsilometer test (Etest) and for amoxicillin by an agar dilution method only. 27% strains were resistant to Metronidazole, 3% were resistant Clarithromycin, no resistance to Amoxicillin was found.

Another study from Brazil, 54% Resistant to Metronidazole, 4% to Tetracycline 13% to Furazolidone.

Another study from Brazil 77.8% were resistant to Metronidazole, 55.8% to Tetracycline, 77.9% to Amoxicillin.[12]

The prevalence of resistant of H. Pylori in present study is very high to Metronidazole, moderate to tinidazone and Amoxicillin and low for ciprofloxaxin, Clarithromycin, tetracycline tinidazole, ornidazole and furazolidone.

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SUMMARY AND CONCLUSION:
1. In Present study was conducted on 60 patients of dyspepsia.
2. In our study, the majority of patients (56.6%) belonged to the age group 35-50 years. There were 47 males (78.3%) and 13 females (21.7%).
3. In our study, most common symptom in H.Pylori infected patients was Pain in upper abdomen (63.3%), 20%) patients had history of Fullness after meal, 16.6% patients had Retrosternal burning pain, 30% patients had nausea,21.6% patients had vomiting, 15% patients had Water brash6.6%o patients had melena,10% had Hemetemesis and 26.6% had Anorexia.
4. In our study In Likert Scale, 28(46.7%) patients had grade II symptoms, 18(30%o) patients had grade III symptoms, 9(15%) patients had grade I symptoms, 5(8.3%) patients had grade IV symptoms.
5. In our study, most patients (90%o) belonged to low socio economical status and most of patients (90%) were consuming untreated water.
6. In our study, 38 cases out of 60 dyspeptic patients gave positive rapid urease test with pyloric antrum biopsy specimens 89.4% cases by RUT were positive within Vi hour, 5.2% took up to 1 hour and remaining 5.2% case become positive within 1 ½ Vi hours, none of case took more than 1 ½ hours in 38 positive cases. This indicates that majority of patients were heavily infected with Helicobacter Pylori (10^6 bacteria/biopsy tissue).
7. In our study, During Endoscopy, Out of total 60 cases, antral gastritis present in 25 patients (41.7%), duodenitis in 13 patients (21.6%), duodenal ulcer in 7 patients 11.6%), gastric ulcer in 4(6.6%) patients.28 (46.6%o) cases upper gastrointestinal Endoscopy was normal.
8. In our study, 100%o duodenal ulcer and 75% of gastric ulcer patients, 88% of gastritis and 76.9%o of duodenitis patients were positive for Helicobacter pylori by RUT and about 32.1% with normal UGI Endoscopy finding dyspeptic patients were RUT positive for H. Pylori.
9. In our study, 68% patients with Antral gastritis, 61.5% patients with duodenitis, 71.4% patients with duodenal ulcer, 50% patients with gastric ulcer were positive by culture method, 28.6% of normal UGI Endoscopy finding dyspeptic patients were culture positive for H. Pylori.
10. The antibiotic resistance of H. Pylori in culture positive cases in our study showed 84.6%o of cases were resistant to Metronidazole, 38.5% to Tinidazole, 7.6%o to Ornidazole, 32.8% to Amoxicillin, 3.8% to Tetracycline, 19.2% to Clarithromycin, 11.5% to furazolidone, and 3.8% to Ciprofloxacin.

CONCLUSION: Our results differed significantly from the few available reports on drug sensitivity profile of H. pylori from other parts of India and world. This finding supports the need for susceptibility testing as a guide to empirical treatment and more generally, to define the resistance patterns of H. pylori in particular geographical area.

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