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Original Article

Comparison of first-line eradication therapy protocols for Helicobacter pylori in regions with high clarithromycin resistance

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Abstract

Aim: First-line eradication therapy protocols for Helicobacter pylori infection and their success rates still prove to be matter of interest for researchers. The aim of this study was to examine retrospectively eradication therapy protocols used in patients infected with H. pylori in our region with high resistance to clarithromycin, compare success rates and determine the factors affecting success rates.
Material and Methods: Eradication therapies for dyspeptic patients who were found to be Helicobacter pylori positive as revealed by upper gastrointestinal endoscopy and biopsy results and success rates attained in the microscopic examination of stool in the 4th week after the therapy were analyzed. Group 1 (legacy triple therapy): clarithromycin 500 mg film-coated tablet 2x1, lansoprazole 30 mg capsule 2x1, amoxicillin 1000 mg tablet 2x1, 14-day therapy period; Group 2 (bismuth-free quadruple therapy): clarithromycin 500 mg film tablet 2x1, rabeprazole 20 mg tablet 2*1, amoxicillin 1000 mg tablet 2x1, metronidazole 500mg 2x1 tablet, 14-day therapy period; Group 3 (bismuthal quadruple therapy): bismuth subsalicylate 262 mg tablet 2x2, metronidazole 500 mg tablet 3x1, tetracycline 500 mg capsule 3x1, pantoprazole 40mg tablet 2x1, 10-day therapy period.
Results: Data of 168 patients were analyzed. The patients were divided into Group 1 (classical therapy) with 80 patients, Group 2 (bismuth-free quadruple therapy) with 46 patients and Group 3 (bismuthal quadruple therapy) with 42 patients. Eradication success rates were as follows: Group 1 (80%), Group 2 (80.4%) and Group 3 (83.3%).
Conclusion: Antibiotic resistance is the sole reason for the low success rate in eradication therapy for Helicobacter pylori.
In regions with high clarithromycin resistance bismuth-free quadruple therapy can be employed as an alternative. In regions with metronidazole resistance in addition to clarithromycin resistance bismuthal therapy protocols can be employed.

Keywords: Helicobacter pylori; eradication therapy; clarithromycin resistance.

INTRODUCTION

Helicobacter pylori (H. pylori) is a microorganism estimated to cause infection in more than 50% of the world population despite its variable prevalence amongst geographical regions. Therefore, it is responsible for considerable rates of morbidity and mortality (1). Eradication of Helicobacter pylori infection continues to be a source of great concern all over the world since it is affiliated with peptic ulcer, stomach cancer and mucosa-associated lymphoid tissue lymphoma (2). The standard recommended therapy in Europe and the USA for H. pylori infection is triple therapy including the administration of proton-pump inhibitors (PPI), clarithromycin and amoxicillin or metronidazole (3,4). While the success rate for eradication was over 90% at the beginning, it fell below 70% in time; one of the reasons for this is the resistance to antibiotics, particularly clarithromycin. In some regions a high rate of clarithromycin resistance is observed among H. pylori strains since clarithromycin is a commonly used medication in the treatment of other infections (1,5). Clarithromycin resistance prevalence reported in H. pylori varies between 12.5% and 76.2% in different parts of the world (6-10). Present guidelines stress the importance of

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the awareness of regional H. pylori resistance patterns and advise that therapeutic regimens should be used in a region that can attain at least 90% success rate (5,11). Various therapeutic designs have been recommended to increase eradication rates (12). In recent studies clarithromycin resistance rates in Turkey have been found to be 36.7%-47.5%-48.2% respectively (13-15). Due to high clarithromycin resistance in first-line eradication therapy, bismuth-free quadruple therapy (PPI, clarithromycin, amoxicillin, metronidazole) and bismuthal quadruple therapy (PPI, bizmopen, metronidazole, tetracycline) are employed as an alternative to legacy triple therapy.

The aim of this study was to examine retrospectively the protocols of eradication therapies used in patients infected with H. pylori in our region with high resistance to clarithromycin, compare success rates and determine the factors affecting the success rates.

MATERIAL and METHODS

Patients

In the present study the data of patients over 18 years of age, who presented to our Gastroenterology and Gastroenterological Surgery Polyclinics with complaints of dyspepsia between January 2017 and August 2018, were retrospectively analyzed. Patients diagnosed to be Helicobacter pylori positive as revealed by upper gastrointestinal endoscopic biopsy results whose post-therapy eradication control was maintained by means of Helicobacter pylori antigen found directly in the stool were included in the study. Group 1 (classical triple therapy): clarithromycin 500 mg film-coated tablet 2x1, lansoprazole 30 mg capsule 2x1, amoxicillin 1000 mg tablet 2x1, 14-day therapy period; Group 2 (bismuth-free quadruple therapy): clarithromycin 500 mg film tablet 2x1, rabeprazole 20 mg tablet 2*1, amoxicillin 1000 mg tablet 2x1, metronidazole 500mg 2x1 tablet, 14-day therapy period; Group 3 (bismuthal quadruple therapy): bismuth subsalicylate 262 mg tablet 2x2, metronidazole 500 mg tablet 3x1, tetracycline 500 mg capsule 3x1, pantoprazole 40mg tablet 2x1, 10-day therapy period. Patients who received different therapy protocols owing to peptic ulcer, chronic liver and kidney failure, those who previously received H. pylori eradication therapy, those with a history of malignancy and those who had antibiotic treatment within the last 4 weeks due to other reasons and those who had to quit therapy and adopt a different therapy protocol were not included in the study.

Procedure

The data of patients receiving eradication therapy were retrospectively analyzed. Patients who received three different therapy protocols were evaluated in terms of age, sex, smoking, body mass index (BMI), rate of helicobacter pylori positivity, intestinal metaplasia, comorbidity (diabetes, high blood pressure, coronary artery disease) and post-therapy eradication. All patients received upper gastrointestinal endoscopy examination at the endoscopy unit of our hospital. Histological examination was analyzed according to the modified Sydney classification. Accordingly, the following grading was adopted: 1+ mild, 2+ moderate and 3+ severe. Eradication control was carried out 4 weeks after the end of the therapy at the same place by means of direct helicobacter antigen in the stool.

Board of ethics approval for this study was obtained from the ethics commission of our hospital. Approval no: 2018.9/3-142. Approval date: 20.12.2018.

This study is retrospective and therefore no consent form.

Statistical Analysis

Statistical analysis was performed by the SPSS 22.0 software (SPSS Inc.; Chicago, IL, USA). Factors which were assumed to be contributing to the existence of antigen in the stool (in the evaluation of response to treatment) such as sex, age, (age>50), BMI (BMI>30), antral gastritis, erosive gastritis, erosive bulbitis, rate of H. pylori positivity, existence of metaplasia, therapy groups, smoking and comorbidities were taken into consideration (with a view to see if there was a cause-effect relationship). The values P<0.25 in the comparison of groups were included in the analysis and in addition multivariate logistic regression was used for therapies offered. The factors affecting the therapy outcome were analyzed by forming 3 groups. In Model 1 comorbidity, sex and therapy groups' response to antigen in the stool were statistically analyzed. In the logistic regression model no significant relation was found (p>0.05). It was concluded that comorbidity and sex in Model 2 and therapy groups in the last model (Model 3) did not affect the antigen response in the stool. In the logistic regression analysis, it was observed that both models (Model 2 and 3) were far from having statistically significant difference on the consequence of the therapy (antigen in the stool) (p>0.05). That 3 different therapy groups, especially in Model 3, did not statistically change the antigen in the stool proved that each therapy alternative could be employed. Statistical significance was set at P <0.05.

RESULTS

The data of a total of 243 patients were retrospectively analyzed. 32 patients who received another therapy protocol (different PPI or different antibiotic regimen), 3 patients who switched to a different protocol owing to intolerance to bismuthal protocol, 21 patients who had been earlier administered eradication therapy and 19 patients who were lost to follow-up (did not show up for controls) were excluded from the study. Therefore, the data of 168 patients were analyzed. Group 1 (legacy triple therapy) contained 80 patients, Group 2 (bismuth-free quadruple therapy) 46 patients and Group 3 (bismuthal quadruple therapy) 42 patients. Clinical data and microscopic findings pertaining to patients have been presented in Table 1. The following eradication success rates were found respectively for Group 1 (80%), Group 2 (80.4%), Group 3 (83.3%); no statistically significant difference was observed (p: 0.935). Table 2 shows the results of statistical comparison of parameters among the 3 groups.

Table 1. Risk factors for Helicobacter antigen in stool

							95% C.I.for EXP(B)		
		B	S.E.	Wald	df	Exp(B)	Lower	Upper	P value
Model 1	Co-morbidity	.229	.769	.088	1	1.257	.278	5.675	.766
	Gender	.931	.847	1.210	1	2.538	.483	13.339	.271
	Group 1	-.497	.867	.329	1	.608	.111	3.326	.566
	Group 2	-237	1.339	.031	1	.789	.057	10.874	.859
	Constant	-2.190	1.477	2.199	1	.112			.138
Model 2	Co-morbidity	191	.755	.064	1	1.210	.275	5.318	.800
	Gender	892	.833	1.148	1	2.441	.477	12.489	.284
	Constant	-.2.532	.762	11.040	1	.080			.001
Model 3	Group 1	-.223	.500	.200	1	.800	.301	2.130	655
	Group 2	-.196	.556	.124	1	.822	.276	2.447	.725
	Constant	-.1.191	.623	3.656	1	.304			.056

Table 2. Clinical and microscopic characteristics

	n (%)
Age	45.1±10 (24-67)
Gender	
Male	53 (31.5)
Female	115 (68.5)
BMI (kg(m2)	26.9 (19.4-42.1)
Smoker	26 (15.4)
Co-Morbidity	
Hypertension	13 (7.7)
Diabetes mellitus	12 (7.11)
Coronary artery disease	9 (5.3)
None	49 (29.1)
NA	93 (55.3)
Gastritis	
Antral gastritis	131 (77.9)
Erosive gastritis	21 (12.6)
Pan-gastritis	16 (9.5)
Number of biopsy (Antrum)	
1	59 (35.1)
2	85 (50.5)
3	17 (10.1)
4	7 (4.1)
Number of biopsy (Antrum + corpus)	36 (21.4)
Positivity of H. pylori	
+	134 (79.7)
++	20 (11.9)
+++	14 (8.3)
Metaplasia	
Yes	17 (10.1)
No	151 (89.9)
Treatment	
Classical triple therapy	80 (47.6)
Quadruple therapy without Bi	46 (27.5)
Quadruple therapy with Bi	42 (25)
H. pylori Ag in stool	
Yes	32 (19)
No	136 (81)

Ag: Antigen, Bi: Bismuth, BMI: (Body Mass Index), H. pylori: Helicobacter pylori, NA: Not Available

Table 3. Comparison of the clinical and microscopic parameters in groups

	Classical triple therapy (n=80)	Quadruple therapy without Bi (n= 46)	Quadruple therapy with Bi (n=42)	P-value
Age	45±11	46.7±9.	43.3±8.6	0.27
Gender				0.108
Male	27 (33.7%)	28 (60.9%)	34 (81%)	
Female	53 (66.3%)	18 (39.1%)	8 (19%)	
BMI (kg/m2)	26.8 (19.4-42.1)	26.3 (22.8-34.5)	29.1 (20.4-40)	0.75
Smoker	21 (28%)	1 (1.3%)	4 (5.3%)	0.05
Co-morbidity	14 (8.3%)	3 (1.8%)	9 (5.4%)	0.001
HT	7 (9.3%)	1 (1.3%)	5 (6.7%)	0.446
DM	8 (10.7%)	0 (0%)	4 (5.3%)	0.351
CAD	3 (4%)	2 (2.7%)	4 (5.3%)	0.102
Gastritis				
Antral gastritis	61 (36.3)	38 (22.6)	32 (19)	0.677
Erosive gastritis	12 (7.1)	5 (3)	4 (2.4)	0.631
Pan-gastritis	7 (4.2)	3 (1.8)	6 (3.6)	0.463
Positivity of H. pylori				
+	61 (36.3)	35 (20.8)	38 (22.6)	0.153
++	10 (6)	7 (4.2)	3 (1.8)	0.505
+++	9 (5.4)	4 (2.4)	1(0.6)	0.243
Metaplasia				0.01
Yes	11 (6.5)	0	6 (3.6)	
No	69 (41.1)	46 (27.4)	36 (21.4)	
H. pylori Ag in stool				0.935
Yes	16 (9.5)	9 (5.4)	7 (4.2)	
No	64 (38.1)	37 (22)	35 (20.8)	

Ag: Antigen, BMI: Body Mass Index, CAD: Coronary Artery Disease, DM: Diabetes mellitus, H. Pylori: Helicobacter pylori, HT: Hypertension

Table 4. Clinical and microscopic features in terms of treatment result (H. pylori Ag in stool)

	H. pylori Ag in stool (-) (n=136)	H. pylori Ag in stool (+) (n=32)	P-value
Age	46.1 +(10.3)	44.5 +9.8	0.618
Gender			0.083
Male	47 (28)	6 (3.6)	
Female	89 (53)	26 (15.5)	
BMI (kg/m2)	27.9+5	26.4+6.6	0.410
Smoker	23 (30.7)	3 (4)	NS
Co-morbidity	23 (13.7)	3 (1.8)	0.229
Gastritis			
Antral gastritis	106 (63.1)	25 (14.9)	0.982
Erosive gastritis	18 (10.7)	3 (1.8)	0.768
Pan-gastritis	12 (7.1)	4 (2.4)	0,510
Positivity of H. pylori			
+	109 (64.9)	25 (14.9)	0.798
++	15 (8.9)	5 (3)	0.543
+++	12 (7.1)	2 (1.2)	NS
Metaplasia			0.533
Yes	15 (8.9)	2 (1.2)	
No	121 (72)	30 (17.9)	
	H. pylori Ag in stool (-) (n=136)	H. pylori Ag in stool (+) (n=32)	P-value
Age	46.1 +(10.3)	44.5 +9.8	0.618
Gender			0.083
Male	47 (28)	6 (3.6)	
Female	89 (53)	26 (15.5)	
BMI (kg/m2)	27.9+5	26.4+6.6	0.410
Smoker	23 (30.7)	3 (4)	NS
Co-morbidity	23 (13.7)	3 (1.8)	0.229
Gastritis			
Antral gastritis	106 (63.1)	25 (14.9)	0.982
Erosive gastritis	18 (10.7)	3 (1.8)	0.768
Pan-gastritis	12 (7.1)	4 (2.4)	0,510
Positivity of H. pylori			
+	109 (64.9)	25 (14.9)	0.798
++	15 (8.9)	5 (3)	0.543
+++	12 (7.1)	2 (1.2)	NS
Metaplasia			0.533
Yes	15 (8.9)	2 (1.2)	
No	121 (72)	30 (17.9)	

Ag: Antigen, BMI: Body Mass Index, H. Pylori: Helicobacter pylori, NS: Non-specific, HT: Hypertension

Table 5. Correlation results

		age	Sex 0 female 1 male	antral gastritis	erosive bulbit	pan gastritis	h.pylori (1:+, 2:++, 3:+++)	metaplasiai?	Therapy 1: Classical triple therapy, 2: Quadruple therapy without Bismuth, 3: Quadruple therapy with Bismuth	kg/m2	antigen in the gaita?	is there h1	is there h2	is there h3
age	Pearson Correlation	1	.088	-.053	.052	.016	.167*	.043	-.058	.304**	-.039	-.117	-.024	.198*
	Sig. (2-tailed)		.259	.497	.502	.841	.030	.584	.458	.008	.618	.130	.761	.010
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
Sex 0 female 1 male	Pearson Correlation	.088	1	-.134	.208**	-.046	-.045	.027	-.109	-.193	-.134	.023	.027	-.066
	Sig. (2-tailed)	.259		.084	.007	.556	.562	.728	.158	.098	.084	.766	.725	.398
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
antralgastrit	Pearson Correlation	-.053	-.134	1	-.711**	-.610**	-.128	.083	.011	-.004	.002	.197*	-.248**	.004
	Sig. (2-tailed)	.497	.084		.000	.000	.098	.284	.887	.974	.982	.010	.001	.956
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
erosive bulbit	Pearson Correlation	.052	.208**	-.711**	1	-.123	-,030	-.007	-.071	.019	-.046	-.034	.139	-.114
	Sig. (2-tailed)	.502	.007	,000		,113	.704	.924	.359	.872	.555	.665	.072	.141
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
pangastritis	Pearson Correlation	,016	-,046	-.610**	-.123	1	.214**	-.109	.065	-.015	.049	-.240**	.194*	.122
	Sig. (2-tailed)	,841	.556	.000	.113		.005	.160	.405	.901	.527	.002	.012	.114
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
h.pylori (1:+, 2:++, 3:+++)	Pearson Correlation	.167*	-.045	-.128	-.030	.214**	1	-.060	-.144	-.086	-.004	-.932**	.431**	.849**
	Sig. (2-tailed)	.030	.562	.098	.704	.005		.438	.062	.466	.964	,000	.000	.000
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
metaplazi yes no ?	Pearson Correlation	.043	.027	.083	-.007	-.109	-.060	1	-.028	-.015	-.062	.071	-.062	-.030
	Sig. (2-tailed)	.584	.728	.284	.924	.160	.438		.721	.902	.423	.362	.422	.702
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
Therapy 1: Classical triple therapy, 2: Quadruple therapy without Bismuth, 3: Quadruple therapy with Bismuth	Pearson Correlation	-.058	-.109	.011	-.071	.065	-.144	-.028	1	.046	-.033	.132	-.055	-.127
	Sig. (2-tailed)	.458	.158	,887	.359	.405	.062	.721		.697	.676	.089	.476	.102
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
kg/m2	Pearson Correlation	.304**	-.193	-.004	.019	-.015	-.086	-.015	.046	1	-.097	.066	-.004	-.092
	Sig. (2-tailed)	.008	.098	.974	.872	.901	.466	.902	.697		.410	.573	.970	.432
	N	75	75	75	75	75	75	75	75	75	75	75	75	75
stool antigen?	Pearson Correlation	-.039	-.134	.002	-.046	.049	-.004	-.062	-.033	-.097	1	-.020	.056	-.037
	Sig. (2-tailed)	.618	.084	.982	.555	.527	.964	.423	.676	.410		.799	.473	.638
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
h1 ?***	Pearson Correlation	-.117	.023	.197*	-.034	-240**	-.932**	.071	.132	.066	-.020	1	-.730**	-.599**
	Sig. (2-tailed)	.130	.766	.010	.665	.002	.000	.362	.089	.573	.799		.000	.000
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
h2 ?***	Pearson Correlation	-.024	.027	-.248**	.139	.194*	.431**	-.062	-.055	-.004	.056	-.730**	1	-.111
	Sig. (2-tailed)	.761	.725	.001	.072	,012	.000	.422	.476	.970	.473	.000		.153
	N	168	168	168	168	168	168	168	168	75	168	168	168	168
h3 ?***	Pearson Correlation	.198*	-.066	.004	-.114	.122	.849**	-.030	-.127	-.092	-.037	-.599**	-.111	1
	Sig. (2-tailed)	.010	.398	.956	.141	.114	.000	.702	.102	.432	.638	.000	.153	
	N	168	168	168	168	168	168	168	168	75	168	168	168	168

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed)

There was a statistically significant difference among groups in terms of the presence of comorbidity and metaplasia (p=0.001 and p=0.01, respectively). No significant difference was detected among the groups in terms of age, sex, smoking, gastritis (antral gastritis, erosive gastritis, pan-gastritis), H. pylori positivity and presence of antigen in the stool (p>0.05). Patients were divided into two groups depending on the level of antigen in the stool. These groups did not present any statistically significant differences when compared in terms of age, sex, body mass index (BMI), smoking, comorbidity, gastritis (antral, erosive and pan-gastritis), H. pylori positivity and metaplasia. Table 3 shows the comparison of the patients in terms of antigen presence in the stool. The relation between variables was evaluated based on a correlation. The factors that could affect one another in the Pearson correlation repository were evaluated. It was seen that patients with antral gastritis and pangastritis and H. Pylori positivity could affect each other (increasing each other's effect) statistically (p=0.02 and p=0.002 respectively). (Table 4)

DISCUSSION

In the present study, no significant difference was found between success rates pertaining to legacy triple therapy, bismuth-free quadruple therapy and bismuthal quadruple therapy in the primary Helicobacter pylori eradication therapy of the study population with high clarithromycin resistance.

In recent years, the rate of eradication of H. pylori infection has been gradually going down with standard primary triple therapy (16). Alternative primary therapy methods such as increased medication, extended therapy duration, sequential medication or use of different medication combinations have come to the fore in order to increase the success of eradication (17-21). There are numerous factors that affect therapy for the eradication of H. pylori. These factors include personal, genetic and environmental factors in addition to antibiotic resistance (22). Though some studies point to the role of sex in the response to eradication therapy, some others did not find such a relation (23, 24). In the present study, no statistical evidence was found to show that sex, smoking, body mass index (BMI) and individual comorbidity have any statistical effect on eradication therapy.

In international consensus reports, triple clarithromycin–based therapy is not recommended in countries where clarithromycin resistance is higher than 15% (17-27). Instead, bismuthal quadruple therapy or bismuth-free quadruple therapy is recommended in these regions (27). In the meta-analysis of recent randomized controlled studies, 14-day bismuth-free quadruple therapy has been found to be superior to 14-day legacy triple therapy (17). Likewise, in another randomized controlled study 14-day bismuth-free quadruple therapy has been observed to be akin to 10-day bismuthal quadruple therapy (91.3%-91.6%) (28). In the present study eradication success rates of first-line legacy triple therapy, bismuth-free quadruple therapy and bismuthal quadruple therapy were compared. The results of the study revealed no statistically significant difference.

Recent success rates of legacy triple therapy performed in our country have been found to be rather low. Eradication rate of a one-week therapy has been found to be 46% in one study and the success rate of a two-week legacy triple therapy in another study has been found to be 50-65% (29). Eradication success rate of a randomized controlled study carried out by Özbalcı et al. has been reported to be 53% (30). The results of the present study revealed that the success rate of the legacy triple therapy was 80%. This rate has been considered rather high compared to previous studies. Since the study is a retrospective one and some patients were lost to follow-up, we are of the opinion that the exact eradication rate is much lower than the stated figure.

Since the main reason why resistance appeared in legacy triple therapy was clarithromycin resistance, alternative therapies have been sought. In a randomized prospective study by Liou-Ming et al., the success rate of bismuth-free quadruple therapy was found to be 91.3% (28). Similarly, the success rate of a bismuth-free quadruple therapy in a randomized prospective study by Fernando Marcias et al. was over 90% (31). In the present study, the success rate of bismuth-free quadruple therapy has been found to be lower than the rates in similar studies (80.04%). It may be argued that the reason for this is metronidazole resistance, which has recently been on the rise in Turkey and the world (32).

In the Maastricht V/Florence Consensus guidelines, bismuthal quadruple therapy is recommended in regions where high clarithromycin and metronidazole resistance is observed (33). In recent studies, success rate of bismuthal therapy has been reported to be in the range of 80-95% (33-35). In the study by Özbalcı et al., on the other hand, it has been found to be 78.5% (30). In the present study the success rate of eradication has been found to be 83%. This rate in our study was higher, if not more significant than it was in other studies. However, this rate was lower compared to the studies mentioned above. We believe that the low rate also in the bismuthal group could be dependent on metronidazole resistance in our country.

The limiting factors in our study were that our study was a retrospective one, we failed to have access to information about certain patients and randomization was not equal.

CONCLUSION

Although the clarithromycin resistance in our region was not as high as expected, the success of the treatment with bismuth was found to be lower than expected.

Antibiotic resistance is the sole reason why success rate in Helicobacter pylori eradication therapy was low. Bismuth-free quadruple therapy can be used alternatively in regions where high clarithromycin resistance is seen. Bismuthal therapy protocols can be used in regions

where clarithromycin resistance is seen in addition to metronidazole resistance. We are of the conviction that prospective studies are needed with larger series on clarithromycin and metronidazole resistance.

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