Original Article

The Efficacy of Bismuth Quadruple Therapy, Sequential Therapy, and Hybrid Therapy as a First-Line Regimen for *Helicobacter pylori* Infection Compared with Standard Triple Therapy

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ABSTRACT

Background and Aim: To compare the effectiveness of first-line *Helicobacter pylori* eradication treatments as standard triple therapy (sTT), bismuth-containing quadruple therapy (BQT), sequential therapy (ST), and hybrid therapy (HT). **Patients and Methods:** 303 patients treated between July 2018 and June 2021 were studied. In this study, 76 patients in the sTT group, 78 patients in the BQT group, 75 patients in the ST group, and 74 patients in the HT group were randomly allocated. The diagnosis of *H. pylori* was made endoscopically. *H. pylori* stool antigen test was performed 4 weeks after finishing the treatment. **Results:** The mean age was 48.53 (13.48) in sTT, 49.04 (13.02) in BQT, 48.47 (14.54) in ST, and 47.45 (13.4) in HT. There was no significant age difference among the groups (P = 0.909). *H. pylori* eradication rate in intention-to-treat (ITT) analysis was 68.4% in sTT, 79.5% in BQT, 78.7% in ST, and 83.8% in HT. There was no significant difference between sTT, BQT, and ST regarding of eradication rate. The difference between HT and sTT was significant (P = 0.028). In the per-protocol (PP) analysis, the eradication rate was 74.3% in sTT, 88.6% in BQT, 86.8% in ST, and 92.5% in HT. There was a significant difference between sTT and BQT (P = 0.030) and sTT and HT (P = 0.004), whereas there was borderline significant difference between sTT and ST (P = 0.065). **Conclusion:** In terms of eradication, HT had the best rate, whereas the lowest rate was in the sTT treatment group. This study does not recommend using sTT because of the low eradication rates. This study recommends HT for overcoming antibiotic resistance and better results.

KEYWORDS: *Eradication, Helicobacter pylori, hybrid, sequential, triple*

INTRODUCTION

Helicobacter pylori eradication prevents or treats peptic ulcer disease (PUD), MALT-lymphoma, and gastric adenocarcinoma.[1] The prevalence and clinical outcomes in patients infected with *H. pylori* vary between populations and geographic regions. In many parts of the world, eradication rates are unacceptable.[2-6]

Therefore, many studies investigated the efficacy of alternative first-line treatments to standard triple therapy (sTT). These are bismuth-based quadruple therapy (BQT), sequential therapy (ST), concomitant therapy (CT), and hybrid therapy (HT) that are included in the current guidelines.[6-10] sTT is widely used in Europe and the USA since 1997.[11]

This study aimed to compare the effectiveness of first-line *H. pylori* eradication treatments, such as sTT, BQT, ST, and HT.

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Subjects and Methods

Study design and study population

This study was conducted as a retrospective analysis of the collected data. It was planned as a single-center study. It was held in a tertiary hospital's gastroenterology clinic between July 2018 and June 2021.

All *H. pylori*-infected adult patients were diagnosed endoscopically. Subjects were selected from PUD, gastroeesophageal reflux disease (GERD), and dyspepsia patients. Patients diagnosed with *H. pylori* infection according to the pathological results were included.

The exclusion criteria were being adolescents under the age of 18, having drug allergies, previously taking *H. pylori* eradication therapy, having severe comorbidities, such as decompensated liver cirrhosis, renal failure, pregnancy, and gastric cancer. The demographic data of the participants (age, gender, body mass index (BMI), diagnosis, diabetes mellitus, (DM), hypertension (HT), smoking, chronic obstructive pulmonary disease (COPD), hepatitis, endoscopic findings, and pathological data) were recorded.

The primary endpoint of treatment was the analysis of the Intention to treat (ITT) and per-protocol (PP). The secondary endpoints were adverse events and compliance.

Confirmation of *H. pylori*

Upper gastrointestinal endoscopy of patients with PUD, GERD, and dyspepsia was performed. The biopsy material taken from the stomach that was stained with Giemsa stain was evaluated by different expert pathologists.

Therapy

sTT, BQT, ST, and HT regimens were applied to patients with *H. pylori* infection. A letter containing the instructions was given to all the patients. The patients were advised to read this article. In the sTT treatment regimen, lansoprazole 30 mg p.o. bid, amoxicillin 1000 mg p.o. bid, and clarithromycin 500 mg bid p.o. were used for 2 weeks. In BQT treatment regimen, lansoprazole 30 mg p.o.bid, amoxicillin 1000 mg p.o. bid, clarithromycin 500 mg p.o. bid, and bismuth subsalicylate 262 p.o. qid tb were used for 2 weeks. In the ST regimen, the first 5 days (days 1–5) esomeprazole 40 mg p.o. bid and amoxicillin 1 g p.o. bid; the next 5 days (days 6–10) esomeprazole 40 mg p.o. bid, clarithromycin 500 mg p.o. bid, and metronidazole 500 mg p.o. bid were used. In the HT treatment regimen, first week, esomeprazole 40 mg p.o. tb bid and amoxicillin 1000 mg p.o. bid; second week, esomeprazole 40 mg p.o. bid, amoxicillin 1000 mg p.o. bid, clarithromycin 500 mg p.o. bid, and metronidazole 500 mg p.o. bid were used. The study design was shown in Figure 1.

Adverse events and compliance

Those who received less than 80% of the drug were considered non-compliant. Adverse events were defined as unexpected symptoms that developed up to 4 weeks after the beginning of treatment. Adverse events were divided into mild, moderate, and severe (requiring discontinuation of treatment).

Confirmation of *H. pylori* eradication

H. pylori stool antigen test was performed 4 weeks after finishing the treatment. It was ensured that Proton Pump Inhibitors (PPI) and antibiotics were discontinued at least 2 weeks before the test so that patients could get accurate results. *H. pylori* stool antigen was analyzed with CITEST (Canada) *H. pylori* Antigen Rapid Test Cassette (Feces).

Statistical analysis

Shapiro–Wilk's test was used for the homogeneity of the groups. Fisher's Freeman Halton exact test and Chi-square test were used for differences in demographic data, eradication rates, pathological data, and adverse events between different treatment regimens. ANOVA test was used for age in demographic data and the compliance results. Kruskal–Wallis test was used for BMI. The Chi-square test was used for ITT and PP analysis. The statistical analysis was performed with SPSS (version 25 for Microsoft Windows, IBM, Chicago, IL, United States). $P < 0.05$ was considered significant.

Ethical consideration

This study was conducted as a retrospective analysis of the data collected prospectively. It was approved by the Local Ethics Committee with the letter numbered E-17073117-050.06 dated 06/22/2021.

Results

Patients characteristics

A total of 324 patients with *H. pylori* (+) diagnosed with PUD, GERD, and dyspepsia were evaluated. While 15 of 21 patients who were not included in the study met the exclusion criteria, 6 patients refused treatment [Figure 1]. A total of 303 patients were included in the ITT analysis and 275 patients were included in the PP analysis. About 76 patients in the sTT group, 78 patients in the BQT group, 75 patients in the ST group, and 74 patients in the HT group were randomly allocated. Compliance was defined as taking more than 80% of the drugs. The mean age was 48.53 (13.48) in sTT, 49.04 (13.02) in BQT, 48.47 (14.54) in ST, and 47.45 (13.4) in HT. There was no significant age difference among the

Table 1: Baseline characteristics of study population

Parameter	sTT	BQT	ST	HT	*P*
Number of patients	76	78	75	74	
Age (Mean, SD)	48.53 (13.48)	49.04 (13.02)	48.47 (14.54)	47.45 (13.4)	0.909[a]
Male/Female	24/52	36/42	32/43	40/34	0.045[b]*
Body Mass Index (kg, m²/SD)	26.91 (3.96)	27.11 (4.19)	27.32 (4.31)	27.26 (3.81)	0.960[c]
Smoking	25 (32.9%)	13 (16.7%)	24 (32%)	14 (18.9%)	0.031[b]*
Diabetes Mellitus	13 (17.1%)	8 (10.3%)	11 (14.7%)	9 (12.2%)	0.633[b]
Hypertension	20 (26.3%)	19 (24.4%)	17 (22.7%)	19 (25.7%)	0.957[b]
COPD	4 (5.3%)	3 (3.8%)	1 (1.3%)	5 (6.8%)	0.363[b]
Liver Disease	0 (0%)	2 (2.6%)	0 (0%)	2 (2.7%)	0.289[b]
Endoscopic Finding					
LES Failure	36 (28.6%)	40 (31.7%)	28 (22.2%)	22 (17.5%)	0.030[b]*
Hiatal Hernia	3 (13.6%)	7 (31.8%)	5 (22.7%)	7 (31.8%)	0.526[b]
Esophagitis	13 (22.8%)	13 (22.8%)	12 (21.1%)	19 (33.3%)	0.418[b]
Antral Gastritis	41 (32.3%)	35 (27.6%)	26 (20.5%)	25 (19.7%)	0.039[b]*
Pangastritis	21 (21%)	23 (23%)	28 (28%)	28 (28%)	0.418[b]
Erozive Gastritis	11 (22.4%)	12 (24.5%)	16 (32.7%)	10 (20.4%)	0.587[b]
Gastric Ulcer	3 (25%)	4 (33.3%)	1 (8.3%)	4 (33.3%)	0.536[b]
Duodenitis	2 (18.2%)	4 (36.4%)	1 (9.1%)	4 (36.4%)	0.491[b]
Erozive Duodenitis	4 (33.3%)	2 (16.7%)	2 (16.7%)	4 (33.3%)	0.717[b]
Duodenal Ulcer	1 (7.1%)	5 (35.7%)	4 (28.6%)	4 (28.6%)	0.409[b]
F/U loss/Dropout	3 (3.8%)	4 (5.1%)	3 (4%)	3 (3.99%)	

sTT=standard triple therapy, BQT=bismuth-containing quadruple therapy, ST=sequential therapy, HT=hybrid therapy, SD=Standard deviation, COPD=Chronic obstructive pulmonary disease, LES=Lower esophageal sphincter, F/U=Follow-up. Data presented as Whole number and percentage [a] Anova test, [b]Fisher's Freeman Halton Exact test, [c]Kruskal–Wallis test, *P<0.05 significant

Table 2: Pathological characteristics of study population

Parameter	sTT *n* (%)	BQT *n* (%)	ST *n* (%)	HT *n* (%)	*P*
Inflammation					0.312[a]
None	7 (9.2)	0 (0.0)	2 (2.7)	3 (4.1)	
Mild	44 (57.9)	47 (60.3)	49 (65.3)	44 (59.5)	
Moderate	20 (26.3)	27 (34.6)	20 (26.7)	21 (28.4)	
Marked	5 (6.6)	4 (5.1)	4 (5.3)	6 (8.1)	
Activation					0.17[a]
None	26 (34.2)	8 (10.3)	14 (18.7)	12 (16.5)	
Mild	35 (46.1)	50 (64.1)	47 (62.7)	37 (50.7)	
Moderate	13 (17.1)	16 (20.5)	10 (13.3)	23 (31.5)	
Marked	2 (2.6)	4 (5.1)	4 (5.3)	1 (1.4)	
Metaplasia	6 (7.9)	8 (10.3)	13 (17.3)	16 (21.6)	0.062[a]
Atrophy	8 (10.5)	5 (6.4)	6 (8)	6 (8.1)	0.846[a]
Lymphoid follicle	5 (6.6)	4 (5.1)	7 (9.3)	7 (9.5)	0.672[a]
Lymphoid aggregate	5 (6.6)	1 (1.3)	5 (6.7)	9 (12.3)	0.046[a]*

sTT=standard triple therapy, BQT=bismuth-containing quadruple therapy, ST=sequential therapy, HT=hybrid therapy. [a]Fisher's Freeman Halton Exact test. *P<0.05 significant

Table 3: Clinical outcomes of study population

Parameter	sTT	BQT	ST	HT	*P*
Eradication Rate					
Intention-to-treat *n*	68.4%(52/76)	79.5%(62/78)	78.7%(59/75)	83.8%(62/74)	
Per-protocol *n*	74.3%(52/70)	88.6%(62/70)	86.8%(59/68)	92.5%(62/67)	
Compliance >80%	95.9%(70/73)	94.6%(70/74)	94.4%(68/72)	94.4% (67/71)	0.968[a]

sTT=standard triple therapy, BQT=bismuth-containing quadruple therapy, ST=sequential therapy, HT=hybrid therapy. Chi-squared test was used for intention-to-treat and per-protocol analysis. [a]Fisher's Freeman Halton Exact test. P<0.05 significant

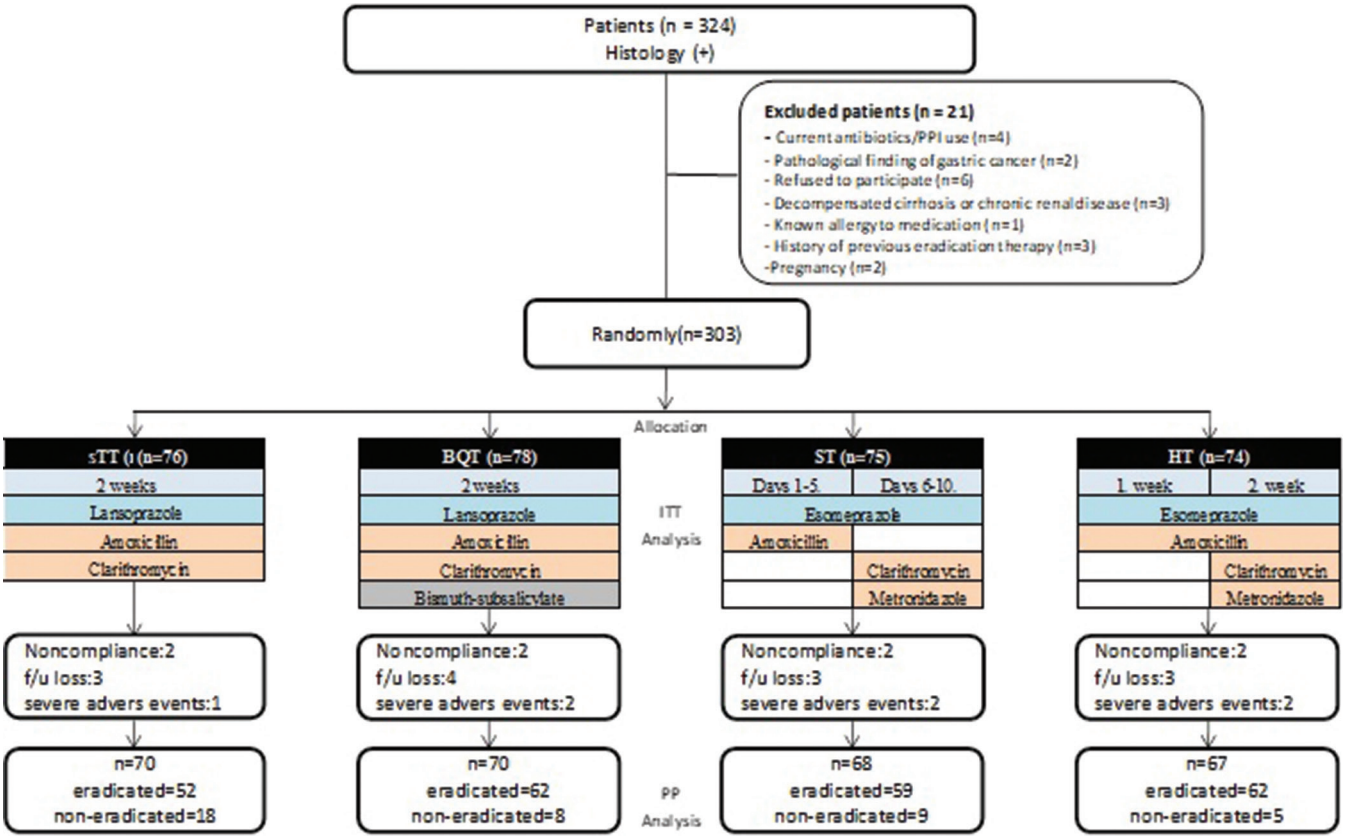

Figure 1: The study design

Table 4: Analysis of all adverse events of the study population

	sTT	BQT	ST	HT	*P*
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Parameter					
Abdominal pain	1 (1.4)	5 (6.8)	4 (5.6)	4 (5.6)	0.779[a]
Headache	2 (2.7)	4 (5.4)	2 (2.8)	2 (2.8)	0.474[a]
Vomiting	0 (0)	1 (1.4)	1 (1.4)	2 (2.8)	0.667[a]
Diarrhea	2 (2.7)	3 (4.1)	2 (2.8)	2 (2.8)	0.996[a]
Constipation	0 (0)	1 (1.8)	1 (1.8)	0 (0)	0.871[a]
Bitter taste	7 (9.6)	7 (9.6)	4 (5.6)	4 (5.6)	0.684[a]
Fecal discoloration	0 (0)	4 (5.4)	0 (0)	0 (0)	0.015[a]*
Black tongue	0 (0)	4 (5.4)	0 (0)	0 (0)	0.015[a]*
Skin rash and pruritis	1 (1.4)	0 (0)	2 (2.8)	1 (1.4)	0.555[a]
Overall					0.826[a]
Mild	11 (15.1)	7 (9.5)	7 (9.7)	6 (8.5)	
Moderate	1 (1.4)	5 (6.8)	3 (4.2)	2 (2.8)	
Severe	1 (1.4)	2 (2.7)	2 (2.8)	2 (2.8)	

sTT=standard triple therapy, BQT=bismuth-containing quadruple therapy, ST=sequential therapy, HT=hybrid therapy. [a]Fisher's Freeman Halton Exact test. **P*<0.05 significant

groups (P = 0.909). Baseline characteristics of the study population and pathological characteristics were shown in Tables 1 and 2.

H. pylori eradication rate in ITT analysis was 68.4% in sTT, 79.5% in BQT, 78.7% in ST, and 83.8% in HT. There was no significant difference between sTT, BQT, and ST regarding eradication rate. The difference between HT and sTT was significant (P = 0.028). Clinical outcomes of the study population were shown in Table 3.

In the PP analysis, the eradication rate was 74.3% in sTT, 88.6% in BQT, 86.8% in ST, and 92.5% in HT. There was a significant difference between sTT and BQT (P = 0.030) and sTT and HT (P = 0.004), whereas there was a borderline significant difference between sTT and ST (P = 0.065). There was no significant difference among BQT, ST, and HT in PP analysis [Table 3]. Analysis of all adverse events of the study population was shown in Table 4.

Compliance

The compliance was 95.9% in sTT, 94.6% in BQT, 94.4% in ST, and 94.4% in HT. There was no significant difference among the treatment regimens (P = 0.968) concerning compliance.

Discussion

H. pylori is a gram-negative and urease-positive bacteria that cause PUD, MALToma, and gastric adenocarcinoma. Various treatment regimens are used for *H. pylori* infection. Eradication rates are gradually

decreasing in first-line treatment regimens. In the sTT regimen, eradication rates decreased to 60–70%. In primary care eradication, various treatment regimens are developed. Efforts are made to increase eradication rates. As the number of antibiotics used in treatment regimens increases, compliance decreases and side effects increase. Because of the decreased eradication rates in sTT regimen, efforts were made to exclude the sTT regimen from primary care in recent years.[7] The optimal duration of the BQT and ST regimens remains unclear. These regimens are most commonly used for 10–14 days in routine clinical practice.

According to the Maastricht Consensus Conference, the aimed eradication rates should be more than 80% for ITT and 90% for PP.[12] In a systematic study conducted in Canada, the ITT rate was 45.2% and PP rate was 63.6% for 10-daysTT regimen, whereas ITT rate was 82.7%, and PP rate was 91.5% for 14-day sTT regimen.[13] The 14-day sTT regimen has shown a significantly increased eradication rate in comparison to the 10-days sTT treatment regimen in their study.[13] In a study conducted by Kim *et al*.[14] with 178 patients, ITT was 64.4%, PP was 78.5%, and treatment compliance was 81.5% with a 7-day sTT treatment regimen. In a study conducted by Lavín *et al*.[15] with 60 of 300 patients in which they evaluated the sTT regimen, they found ITT 70%, PP 72%, and compliance 99.6%. However, in this study, omeprazole was used instead of lansoprazole. The findings of this study had similarities and differences with those in other quoted studies regarding compliance to therapy, ITT, and PP. There was no difference in compliance with other first-line therapies in this study that used the 14-day therapy regimens. In ITT analysis, the HT regimen had a significant difference from sTT regimen, whereas ST and BQT had no significant difference. In the PP analysis, this study found lower eradication rates than other first-line treatments. Clarithromycin resistance may be the major factor causing failure of the sTT.

The BQT regimen is recommended in both the Second Asian-Pacific Consensus Report and the Maastricht V/ Florance Consensus Report. Bismuth has been shown to have a bactericidal effect and resistance to bismuth does not develop. There is a synergism between bismuth and antibiotics. It is recommended in areas with a high clarithromycin resistance. Bismuth administration sensitizes the *H. pylori* in metronidazole-resistant *H. pylori* infection.[16] Quadruple therapy containing bismuth can provide more than 90% eradication.[17] In a study by Kim *et al*.,[18] 175 patients were given a 10-day BQT regimen and the eradication rate was 74.3% in ITT and 92.9% in PP, which was superior to the 7-day sTT regimen. In a study by Özer Etik *et al*.,[19] 10- and 14-day BQT were compared. About 54 subjects were included in each protocol. In the 10-day and 14-day BQT regimens, ITT was 87% and 85%, PP was 96% and 92%, respectively. In this study, a 14-day regimen was used in BQT group. The eradication rate was 79.5% in ITT and 88.6% in PP. The results of this study were compatible with the literature. There was no significant difference in the ITT analysis and compliance with other treatment regimens, whereas there was a significant difference in PP with sTT regimen. The compliance rate was 94.6%.

In a meta-analysis of six randomized prospective studies that compare ST and sTT on 1759 adult patients in Korea, ITT was 79.4%, PP was 86.4%, and the relative risk was 1,761. As a result of this study, ST did not give high results as expected and could not provide therapeutic significance.[20] Changes in the prevalence of antibiotic resistance lead to conflicting results in efficacy among the treatment regimens.[21,22] In addition, the prevalence of clarithromycin and metronidazole resistance differs in different geographical regions. It is expected to change over time even in the same geographic region.[23-25] Because the ST regimen was more effective in clarithromycin-resistant strains, the eradication rate achieved with ST is significantly higher than that achieved with sTT.[24] Although clarithromycin-based sTT was developed because of metronidazole resistance that developed over time, treatment success in this regimen also decreased as a result of inappropriate antibiotic use.[25] In a meta-analysis by Gatta *et al*.,[26] when ST was compared with 14 days sTT, bismuth-based, and non-bismuth-based quadruple therapies, ST was not superior to these therapies significantly. In a study by Liou *et al*.,[27] ST was given for 10 days and found ITT and PP were 87% and 90.5%, respectively. In this study, eradication rates with ST were 78.7% in ITT, 86.8% in PP, and compliance was 94.4%. There was no significant difference between ST and other treatment regimens in terms of eradication rate and compliance. This was in concordance with the data in the literature.

HT was recommended by Hsu in 2011 to defeat antibiotic resistance. Initial results with this treatment regimen were almost perfect. The eradication rate was 99.1% in PP and 97.4% in ITT.[28] Additionally, Sardarian *et al*.[29] reached better results by the HT than the ST in a region with high antibiotic resistance. In this study, the eradication rates of HT were 83.8% in ITT, 92.5% in PP, and compliance was 94.4%. HT was no different than BQT and ST, whereas it has a significant difference with sTT in terms of ITT (P = 0.028). PP and compliance were not different from other treatment

regimens. ITT and PP in the HT were better than the other treatment regimens.

The strength of this study is that it compares four different first-line eradication regimens. The first limitation of this study is the small number of patients and the fact that is a uni-center. Multicenter and double-blind randomized studies with large numbers of patients are needed for more meaningful results. The second limitation is that antibiotic resistance was not studied. The analysis of antibiotic resistance is expensive and time consuming. The third limitation is that the PPIs used are different. As an example esomeprazole has been reported recently to have better beneficial effects.[30]

In conclusion, there was no difference in compliance between the groups in this study. In terms of eradication, HT had the best rate, whereas the lowest rate was in the sTT treatment group. This study does not recommend using sTT because of the low eradication rates. BQT, ST, and HT give close ratios in ITT and PP analysis. This study recommends HT for overcoming antibiotic resistance and better results.

Key message

This study does not recommend using sTT because of the low eradication rates. BQT, ST, and HT give close ratios in ITT and PP analysis. This study recommends HT for overcoming antibiotic resistance and better results.

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Conflicts of interest

There are no conflicts of interest.

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