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CLINICAL TRIAL REPORT

The Efficacy and Safety of Minocycline-Containing Quadruple Therapies Against *Helicobacter pylori* Infection: A Retrospective Cohort Study

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Background: Minocycline, a derivative of tetracycline, has anti-*Helicobacter pylori* (*H. pylori*) properties and can be used to treat *H. pylori* infection. However, only a few randomized controlled trials (RCTs) have investigated the efficacy of minocycline-containing quadruple therapy (MCQT) in treating *H. pylori* infection. This study aimed to determine the efficacy and safety of MCQT and investigate the factors influencing both aspects.

Methods: This was a retrospective cohort study. Patients diagnosed with *H. pylori* infection between January 1, 2022, and July 31, 2023 at. The primary outcome was the eradication rate of *H. pylori*, and the secondary outcome was the number and type of adverse events.

Results: A total of 828 patients were included in this study. The overall *H. pylori* eradication rate among the included patients at 95% confidence interval (CI) (Range 0.864 to 0.907) was 88.53%. The *H. pylori* eradication rate for patients who received MCQT regimen as the primary therapy was 92.28% (95% CI: 0.901–0.945), significantly higher than that of patients who received MCQT as rescue therapy (80.81%; 95% CI: 0.761–0.855, P=0.003). Adverse events, including dizziness, abdominal distension, diarrhea, nausea, abdominal discomfort, constipation, headache, rash, sleep disorder, palpitation, backache, and anorexia, occurred in 185 (22.34%) patients, with dizziness being the most common (75/828, 9.06%). Compliance with MCQT therapy was an independent factor influencing *H. pylori* eradication in patients receiving MCQT as a primary therapy. Compliance and presence or absence of *H. pylori* infection symptoms at the time of screening were independent factors influencing *H. Pylori* eradication in patients receiving MCQT as rescue therapy. Factors that influenced the occurrence of adverse events included reasons for *H. pylori* infection screening, residence, treatment compliance, and the use of acid-suppressant regimens.

Conclusion: MCQT regimens were effective in *H. pylori* infection eradication, and the treatment resulted only in fewer adverse events when used as primary or rescue therapies for *H. pylori* infection treatment. Future prospective studies with larger sample sizes and more comprehensive data are needed to validate our findings.

Keywords: *Helicobacter pylori*, minocycline, cohort study

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic bacterium that colonizes human gastric mucosa.[1] *H. pylori* causes many diseases, including chronic gastritis, gastric and duodenal ulcers, mucosa-associated lymphoid tissue development, and gastric adenocarcinoma.[2] Currently, triple therapy (proton-pump inhibitor combined with two antibiotics) and bismuth quadruple therapy (proton-pump inhibitor, bismuth, and two antibiotics) are used globally to treat *H. pylori* infection.[3] China is one of the countries with the highest clarithromycin resistance rates in the world.[4] Accordingly, bismuth quadruple therapy has been recommended over triple therapy for initial and second-line *H. pylori* treatment. However, triple therapy is the currently recommended treatment for *H. pylori*.[4] Several studies have shown that the efficacy of BCQT against

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H. pylori infection has gradually decreased[3] in past decades, with antibiotic resistance implicated as one of the main resources.[5] In 2022, Chinese national clinical practice guideline[4] on *H. pylori* treatment recommended high-dose dual therapy (HDDT), a new, improved therapy consisting of amoxicillin (≥3.0 g/day) and PPIs (double dose twice per day or standard dose four times per day) for 14 days as primary and rescue therapy. However, HDDT cannot be used in patients on amoxicillin anaphylaxis and possible occurrence of adverse effects caused by higher dosage. Overall, further studies are needed to yield novel and more effective regimens. This will improve the treatment of H. pylori infection.

Minocycline, a derivative of tetracycline, has a broad-spectrum anti-bactericidal activity against gram-negative and gram-positive, aerobic and anaerobic bacteria. It has been used in treating skin and soft-tissue infections, community-acquired pneumonia, etc.[4] Recent studies have demonstrated that minocycline has anti-*H. pylori* properties and can be used to treat *H. pylori* infection. In 1992, Millar et al[6] demonstrated for the first time the antibacterial properties of minocycline against *H. pylori* in vitro. The ability of minocycline to inhibit *H. pylori* was demonstrated in many more subsequent studies. Additionally, a few studies have also shown that the minocycline resistance rate of *H. pylori* ranges from 0.6%[7] to 6.6%,[8] comparable with that of amoxicillin. Based on these findings, randomized controlled trials (RCTs) have evaluated the efficacy of minocycline-containing quadruple therapy (MCQT) in treating *H. pylori* infection. Studies have indicated that MCQT regimens have a satisfactory killing effect on *H. pylori*. In 2023, Gao et al[9] conducted a systematic review of RCTs on the efficacy and safety of the MCQT for *H. pylori* treatment. This study revealed that the killing efficacy and the rate of occurrence of adverse events related to minocycline quadruple therapy were 83.8% and 35.9%, respectively. Notably, the difference in eradication rate or the occurrence of adverse event rate was not significantly different between the intervention groups and the control groups.[9] Previous RCTs and systematic reviews have provided robust clinical evidence for the efficacy and safety of MCQT in treating *H. pylori* infection. However, evidence on the applicability of the MCQT based on large-scale data is limited owing to the strict eligibility and exclusion criteria used in previous RCTs. Therefore, the individual differences in *H. pylori* eradication outcomes and adverse effects of MCQT on a large scale remain unclear. To address this research gap, this study determined the efficacy and safety of MCQT on *H. pylori* in a large sample and further assessed the factors influencing both.

Materials and Methods

Review Statement and Informed Consent

The protocol for the present study was reviewed and approved by the Ethics Committee of Beijing Jishuitan Hospital. The requisite of obtaining informed consent having been waived in view of the retrospective and observational nature of the study. Waiving of consent does not harm to the rights and interests of included patients. The privacy and personal identity information of included patients were well protected. To sum up, the study was conducted in accordance with the Declaration of Helsinki. The study protocol was registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn) on November 15, 2023 (registration number ChiCTR2300077660).

Study Setting and Data

This retrospective cohort study was conducted at a single center. Only patients who received treatment at the Hospital Information System (HIS) database at the outpatient clinic of Beijing Jishuitan Hospital, Capital Medical University (Beijing, China) between January 1, 2022, and July 31, 2023, were included in the study. Patient data was extracted from the patient files at the hospital.

The current *H. pylori* infection treatment involves therapy and disease clearance progress at the midpoint and end of the treatment period. For the study cohort, a urea breath test was performed within 4–12 weeks after eradication therapy.

The data extracted from patient records included the name, phone number, sex, age at diagnosis, alcohol drinking status, cigarette smoking status, family history of digestive tract tumours, and residence (eg, within or outside the province where the hospital is located). Data were collected from the medical records and telephone calls (when necessary). Clinical information captured included medical history, composition and duration of therapy, frequency of medications, occurrence of adverse events, the qualification of the healthcare provider, and treatment outcomes.

Cigarette-smoking status was defined as consumption of more than ten cigarettes per week in the preceding month. Alcohol consumption status was defined as an alcohol consumption of more than 200g per week in the preceding month.

Study Participants

The inclusion criteria for the study participants were as follows: i. Received *H. pylori* infection therapy regardless of any other underlying complications; ii. Confirmed with *H. pylori* infection before initiation of therapy. *H. pylori* was diagnosed through one or more of the approved tests, including the urea breath test, rapid urease test, and histological staining. Screening for *H. pylori* after the therapy was performed using the urea breath test; iii. Patients who underwent MCQT treatment for *H. pylori* infection. In the present study, MCQT was defined as a quadruple regimen consisting of minocycline combined with another antibiotic, bismuth, and antiacids (a proton pump inhibitor or potassium-competitive acid blocker). It should be pointed out that all included patients received empirical therapy without antibiotic resistance tests and cytochrome P450 2C19 (CYP2C19) polymorphism. The usage and dosage of antibiotics complied with 2022 recommendations by the Chinese National Clinical Practice guideline on *H. pylori* treatment.[4] Minocycline was used instead of amoxicillin, tetracycline, and furazolidone because of the low resistance rate to this drug. Accordingly, patients who received regimens consisting of minocycline (100mg, b.i.d.) plus another antibiotic among levofloxacin (500mg, q.d), amoxicillin (1000mg, b.i.d.) metronidazole (400mg, q.i.d.) and clarithromycin (500 mg, b.i.d.) were selected for further screening. The antacids were selected empirically based on the clinical manifestation of the infection and available antacid options, including rabeprazole (10 mg b.i.d. or 20 mg b.i.d.), esomeprazole (20 mg b.i.d.), and vonoprazan (20mg b.i.d.) for antacids. Besides, bismuth potassium citrate was taken in line with the recommended bismuth dosage of 220 mg, b.i.d.[4]

The following patients were excluded from the study: i patients with incomplete clinical data; ii. patients who underwent MCQT combined with other treatments, such as probiotics and Chinese traditional medicine; and iii. patients who were unable to describe adverse events due to numerous reasons, such as advanced age and mental and psychological abnormalities iv. Patients whose adverse events were caused by other diseases that present with similar symptoms; v. Patients with duplicate records.

Study Outcomes

The primary outcome was the *H. pylori* eradication rate, while the secondary outcomes were the occurrence of adverse events, treatment compliance, and factors influencing the efficacy and safety of MCQT. Compliance was evaluated based on patients' self-reports during follow-up at the midpoint and endpoint of the therapeutic period. Good compliance was defined as intake of at least 90% of the total dosage. The occurrence of adverse event rate was calculated as the percentage of participants with single and/or multiple adverse events relative to the total. In this study, adverse events were defined as all complaints of discomfort that occurred during the treatment period, which were suspected to be drug-related and independent of primary diseases.

Statistical Analysis

This was a retrospective and descriptive study. No formal sample size or power calculation was performed. Categorical variables were presented as frequencies and proportions (%), whereas continuous variables were presented as mean ± Standard Deviation (SD). Categorical data were compared using the chi-squared test or Fisher's exact test. Finally, logistic regression models expressed as adjusted odds ratios (AOR) and corresponding 95% confidence intervals (CI) were calculated to investigate factors influencing the efficacy and safety of MCQT. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corporation, Armonk, NY, USA). Statistical significance was set at a two-sided $P < 0.05$.

Results

Demographic and Clinical Characteristics of Included Participants

A total of 2965 patient records were extracted from the hospital records. After removing 1618 duplicates, 1347 records for an equal number of patients with *H. pylori* infection were processed further. Of the 1347 patients, 341 were excluded

because they had used supplementary therapies, including sequential treatment of digestive ulcers and traditional Chinese medicines. An additional 178 patients were excluded for having incomplete data. Finally, 828 patients were included in the final analysis. (Figure 1) The demographic and clinical data at baseline for patients included in the study are shown in Table 1. The mean age was 40.65±13.15 years. A total of 557 patients underwent primary *H. pylori* eradication therapies, while 271 underwent rescue therapies. The patients could be clustered into three groups based on the treatment received: minocycline-levofloxacin-antacids-bismuth regimen (MLAB) group (n=366), minocycline-amoxicillin-antacids-bismuth regimen (MAAB) group (n=322), and minocycline-metronidazole-antacids-bismuth regimen (MMAB) group (n=140).

H. Pylori Eradication Rates

The overall *H. pylori* eradication rate was 88.53% (95% confidence interval [CI]: range: 0.864-0.907). The eradication rate among patients who received primary therapy was 92.28% (95% CI: 0.901–0.945), higher than 80.81% for patients who received rescue therapy (95% CI; range: 0.761–0.855). The difference in eradication rate was significantly higher in the primary therapy group ($P<0.001$). The eradication rates in the MLAB, MMAB, and MAAB regimen groups as primary therapies were 94.13% (95% CI: 0.915–0.968), 83.95% (95% CI: 0.758–0.921) and 92.90% (95% CI: 0.890–0.968), which was statistically significant. Further pairwise comparison showed that the eradication rate of MLAB and MAAB was significantly higher than that of MMAB (for MLAB vs MMAB, $\chi2=9.046$, $P=0.003$; for MLAB vs MAAB, $\chi2=4.872$, $P=0.027$). No statistically significant differences were found between the MLAB and MAAB groups ($\chi2=0.283$, $P=0.595$) (Figure 2 and Table 2).

The eradication rates of MLAB, MMAB, and MAAB regimens as rescue therapies were 64.41% (95% CI: 0.518–0.770), 83.05% (95% CI: 0.708–0.922) and 86.27% (95% CI: 0.814–0.921), respectively, which were significantly different. Furthermore, pairwise comparison showed that the eradication rate of MMAB and MAAB was significantly higher than

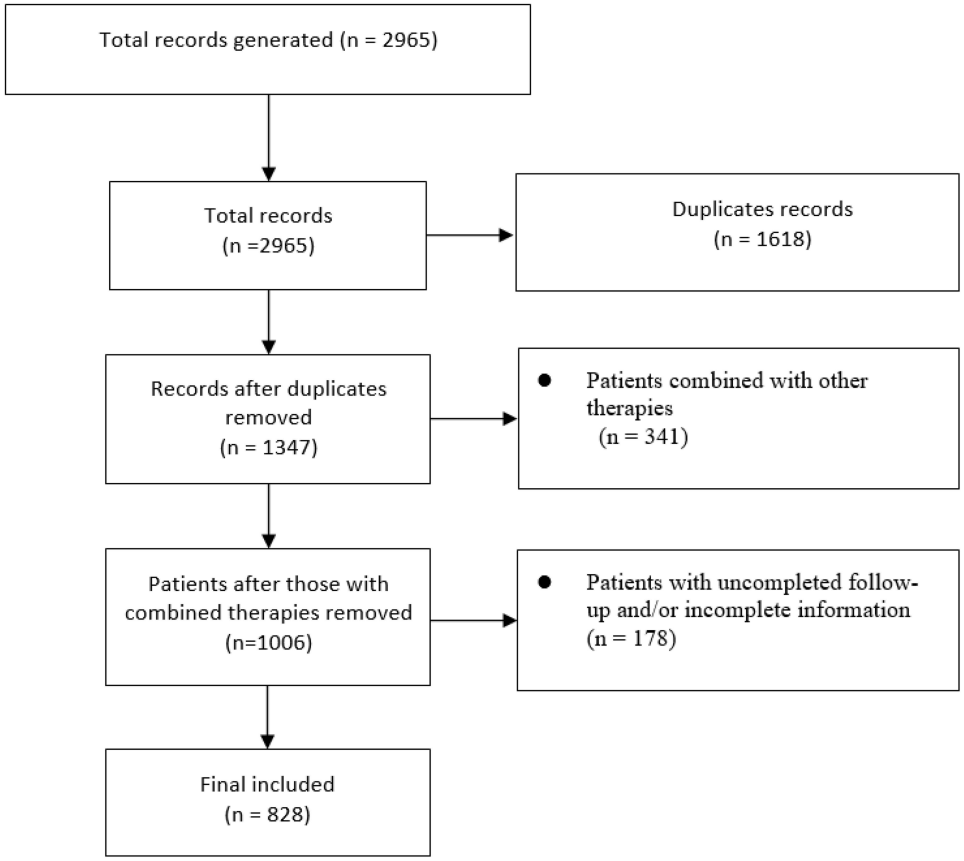

Figure 1 A study flowchart describing the process for identifying included cases.

Table 1 Demographic and Clinical Characteristics of Included Patients

Baseline	Case (n)
Overall	828
Gender	
Male	386
Female	442
Age	
≤20	3
21-30	204
31-40	301
41-50	115
51-60	110
61-70	84
>70	11
Smoking	
Yes	161
No	667
Alcohol intake history	
Yes	155
No	673
Residence (Province)	
Within	697
Outside	131
Reasons for *H. pylori* infection screening	
Screening due to existing symptoms	546
Asymptomatic physical examination	282
Regimens	
MLAB	366
MAAB	322
MMAB	140
Combined acid inhibitors	
Rabeprazole 10mg twice per day	611
Rabeprazole 20mg twice per day	157
Esomeprazole 20mg twice per day	56
Vonoprazan 20mg twice per day	4

Note: Categorical variables are presented as numbers.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

that of MLAB (for MMAB vs MLAB, $\chi 2$=5.294, P=0.021; for MAAB vs MLAB, $\chi 2$=12.817, P<0.001). No significant difference was observed between the MMAB and MAAB groups ($\chi 2$=0.354, P=0.552) (see Figure 2 and Table 2).

Occurrence of Adverse Events

A total of 185 (22.34%) patients reported the occurrence of adverse events, including dizziness, abdominal distension, diarrhea, nausea, abdominal discomfort, constipation, headache, rash, sleep disorder, palpitation, backache, and anorexia. Dizziness was the most common adverse event among all patients, and it occurred in 75 patients (9.06%). The rate of adverse events was higher among patients who received primary therapy than those who received rescue therapy (22.74% vs 21.51%). However, the difference was not statistically significant. The rates for the occurrence of adverse events for the MLAB, MMAB, and MAAB regimens were 21.13% (95% CI: 0.179–0.264), 51.43% (95% CI: 0.430–0.598), and 9.94% (95% CI: 0.067–0.132), respectively. The difference between groups was statistically significant (P<0.001; Table 3).

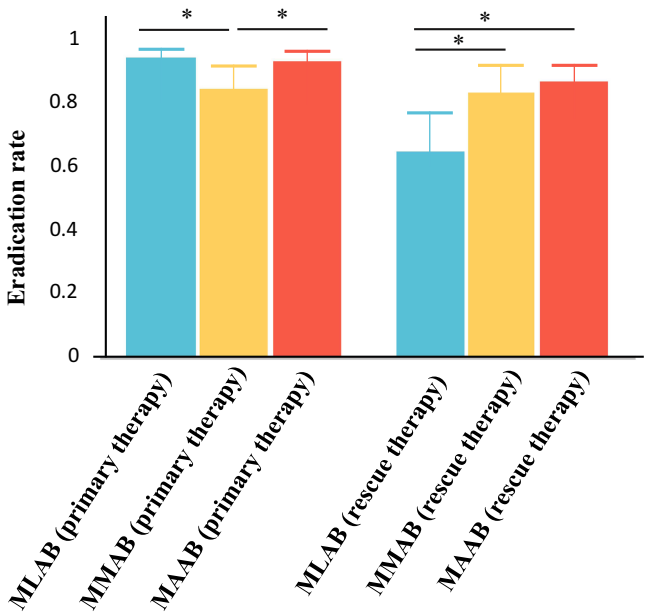

Figure 2 Eradication rates of MCQT regimens in primary and rescue therapies.
Note: *Means $P<0.05$.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

Further pairwise comparisons indicated a statistically significant difference in the occurrence rates of adverse events between the two regimens (eg, MMAB vs MAAB, χ^2=96.297, $P<0.001$; MMAB vs MLAB, χ^2=41.205, $P<0.001$; MLAB vs MAAB, χ^2=18.553, $P<0.001$; Figure 3 and Table 3).

In patients with primary therapy, 128 patients reported the occurrence of adverse events including dizziness, abdominal distension, diarrhea, nausea, abdominal discomfort, constipation, headache, rash, sleep disorder, backache, and anorexia, but not palpitation. The adverse event rates for the MLAB, MMAB, and MAAB regimen groups were 23.13% (95% CI: 0.184–0.279), 46.91% (95% CI: 0.358–0.580), and 11.24% (95% CI: 0.064–0.161), which were statistically different (χ^2=39.373, $P<0.001$). Further pairwise comparisons indicated a statistically significant difference between the two regimens (ie, MMAB vs MAAB, χ^2=39.583, $P<0.001$; MMAB vs MLAB, χ^2=17.951, $P<0.001$; MLAB vs MAAB, χ^2=10.041, P=0.002; Table 4).

Table 2 Eradication Rate of Minocycline-Containing Quadruple Therapies

	n	Eradicated Cases (n)	Eradication Rate	χ2	P
Overall	828	733	88.53% (95% CI: 0.864-0.907)		
Primary therapies	557	514	92.28% (95% CI: 0.901–0.945)		
Rescue therapies	271	219	80.81% (95% CI: 0.761–0.855)	23.606	**<0.001**
Primary therapies					
MLAB	307	289	94.13% (95% CI: 0.915–0.968)[a]		
MMAB	81	68	83.95% (95% CI: 0.758–0.921)		
MAAB	169	157	92.90% (95% CI: 0.890–0.968)[b]	7.108	**0.029**
Rescue therapies					
MLAB	59	38	64.41% (95% CI: 0.518–0.770)		
MMAB	59	49	83.05% (95% CI: 0.708–0.922)[c]		
MAAB	153	132	86.27% (95% CI: 0.814–0.921)[d]	13.375	**0.001**

Notes: Categorical variables are presented as numbers; [a]Compared to MMAB group, χ2=9.046, P=0.003; [b]Compared to MMAB group, χ2=4.872, P=0.027; [c]Compared to MLAB group, χ2=5.294, P=0.021; [d]Compared to MLAB group, χ2=12.817, $P<0.001$.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

Table 3 Adverse Events Among Overall Included Patients

	Dizziness	Abdominal Distension	Diarrhea	Nausea	Abdominal Discomfort	Constipation	Headache	Rash	Sleep Disorder	Palpitation	Backache	Anorexia	Total
Overall (n=828)	75	12	40	38	50	3	7	8	31	1	2	2	185
Primary therapy (n=557)	57	6	25	29	38	1	4	6	21	0	2	2	128
Rescue therapy (n=271)	18	6	15	9	12	2	3	2	10	1	0	0	57
$\chi 2$	2.854	N/A	0.434	1.480	1.842	N/A	N/A	N/A	0.003	N/A	N/A	N/A	0.398
P value	0.095	0.222	0.495	0.288	0.214	0.251	0.689	1.000	1.000	0.327	1.000	1.000	0.594
MLAB regimen (n=366)	25	6	10	13	27	2	2	5	20	1	0	1	81
MMAB regimen (n=140)	42	4	18	17	17	0	2	1	9	0	2	1	72
MAAB regimen (n=322)	8	2	12	8	6	1	3	2	2	0	0	0	32
$\chi 2$	93.632	N/A	23.977	22.400	20.243	N/A	N/A	N/A	N/A	N/A	N/A	N/A	96.827
P value	**<0.001**	0.167	**<0.001**	**<0.001**	**<0.001**	0.645	0.611	0.575	**0.001**	0.532	**0.007**	0.351	**<0.001**

Note: Categorical variables are presented as numbers; A P value in bold means <0.05.

Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

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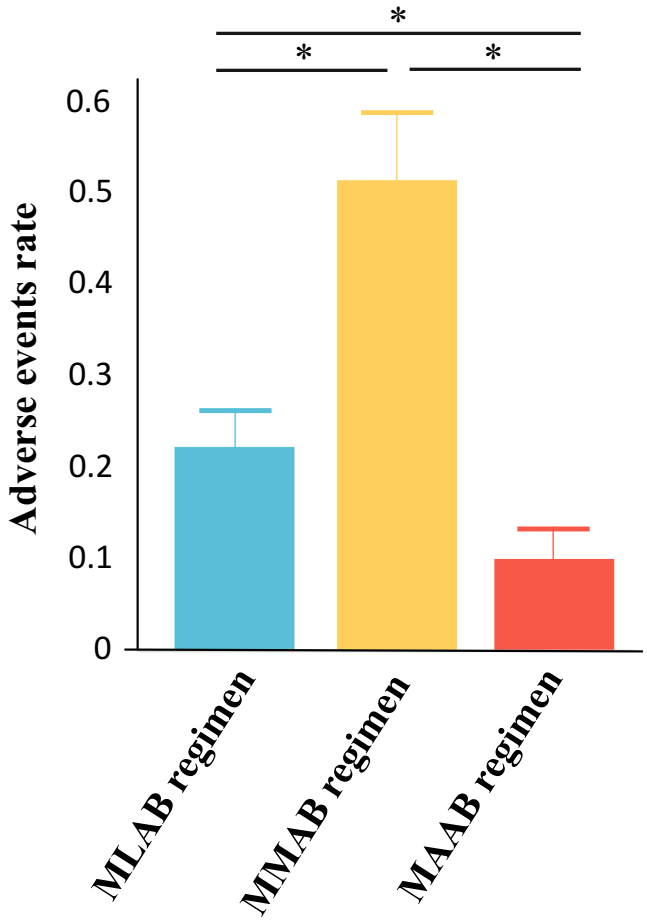

Figure 3 Adverse events rate in MCQT regimens.
Note: *Means $P<0.05$.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

In patients with rescue therapy, 57 patients reported the occurrence of adverse events, including dizziness, abdominal distension, diarrhea, nausea, abdominal discomfort, constipation, palpitation, headache, rash, sleep disorder, but not backache and anorexia (Table 5). The adverse event rates for the MLAB, MMAB, and MAAB regimen groups were 16.95% (95% CI: 0.071–0.268), 57.63% (95% CI: 0.446–0.706), and 8.50% (95% CI: 0.040–0.130), which were statistically significant (χ^2=62.638, $P<0.001$). Further pairwise comparisons indicated a statistically significant difference in the occurrence of adverse events between MMAB and MAAB (χ^2=59.566, $P<0.001$), MMAB and MLAB (χ^2=20.875, $P<0.001$), but not between MLAB and MAAB (χ^2=3.145, P=0.087).

Factors Influencing the Eradication Rate of MCQT

Univariate and multivariate analyses (logistic regression analyses) were performed to identify the factors influencing the eradication rate of the MCQT in patients receiving it as a primary or rescue therapy. For patients receiving MCQT as primary therapy, a significant difference ($P<0.05$) was observed in the eradication rate between good and poor compliant patients. Multivariate logistic regression analyses revealed that poor compliance was significantly associated with failed *H. pylori* eradication (adjusted odds ratio [AOR] =6.944, 95% CI: 2.637–18.288, $P<0.001$; Table 6). For patients using MCQT as a rescue therapy, a significant difference ($P<0.05$) was observed in eradication rates between asymptomatic and symptomatic patients at the time of screening. A significant difference was also observed between patients with good and poor compliance for MCQT as rescue therapy. Multivariate logistic regression analyses indicated that poor

Table 4 Adverse Events Among Patients with Primary Therapy

	Dizziness	Abdominal Distension	Diarrhea	Nausea	Abdominal Discomfort	Constipation	Headache	Rash	Sleep disorder	Backache	Anorexia	Total
MLAB regimen (n=307)	24	5	10	11	23	0	2	5	18	0	1	71
MMAB regimen (n=81)	27	1	7	10	10	0	0	1	2	2	1	38
MAAB regimen (n=169)	6	0	8	8	5	1	2	0	1	0	0	19
$\chi 2$	57.219	N/A	N/A	N/A	8.073	N/A	N/A	N/A	N/A	N/A	N/A	39.373
P value	**<0.001**	0.255	0.113	**0.006**	**0.018**	0.317	0.572	0.255	**0.012**	**0.003**	0.308	**<0.001**

Note: Categorical variables are presented as numbers; A P value in bold means <0.05.

Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

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Table 5 Adverse Events Among Patients with Rescue Therapy

	Dizziness	**Abdominal Distension**	**Diarrhea**	**Nausea**	**Abdominal Discomfort**	**Constipation**	**Headache**	**Rash**	**Sleep Disorder**	**Palpitation**	**Total**
MLAB regimen (n=59)	1	1	0	2	4	2	0	0	2	1	10
MMAB regimen (n=59)	15	3	11	7	7	0	2	0	7	0	34
MAAB regimen (n=153)	2	2	4	0	1	0	1	2	1	0	13
χ**2**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	62.638
P value	**<0.001**	0.235	**<0.001**	**<0.001**	**0.001**	**0.027**	0.153	0.460	**0.001**	0.165	**<0.001**

Note: Categorical variables are presented as numbers; A P value in bold means <0.05.

Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

Table 6 Univariate and Multivariate Analyses for Influencing Factors of Helicobacter Pylori Eradication Rates Among Patients with Primary Therapies

Influencing Factors	Eradication Rate	Univariate Analysis		Multivariate Analysis	
		$\chi 2$	*P1*	AOR	*P2*
Gender					
Male	90.32 (224/248)	2.405	0.121		
Female	93.85 (290/309)				
Age, years					
≤60	92.31 (456/494)	N/A	1.000		
>60	92.06 (58/63)				
Reasons for *H. pylori* infection screening					
Screening due to existing symptoms	94.61 (193/204)	2.448	0.118		
Asymptomatic physical examination	90.93 (321/353)				
Acid suppressant regimen					
Rabeprazole 10mg twice per day	92.07 (395/429)	N/A	0.568		
Rabeprazole 20mg twice per day	94.62 (88/93)				
Esomeprazole 20mg twice per day	87.50 (28/32)				
Vonoprazan 20mg twice per day	100 (3/3)				
Adverse events					
Yes	91.41 (117/128)	0.178	0.671		
No	92.54 (397/429)				
Family history of digestive tumors					
Yes	95.24 (20/21)	N/A	1.000		
No	92.16 (494/536)				
Smoking					
Yes	88.78 (87/98)	2.050	0.149		
No	93.03 (427/459)				
Alcohol intake					
Yes	92.31 (96/104)	0	0.991		
No	92.27 (418/453)				
Residence					
Within province	92.41 (438/474)	0.070	0.792		
Outside province	91.57 (76/83)				
Compliance					
Good	93.28 (500/536)	20.097	**0.001**		
Poor	66.67 (14/21)			6.944 (2.637~18.288)	**<0.001**

Note: Categorical variables are presented as numbers; A P value in bold means <0.05.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

compliance, but not whether were symptomatic or asymptomatic for *H. pylori* infection (AOR=0.526, 95% CI: 0.268–1.030, P=0.061), correlated with failed *H. pylori* eradication (AOR= 11.743, 95% CI: 4.166–33.100, P<0.001; Table 7).

Factors Influencing the Adverse Events Rate of MCQT

Univariate analyses were conducted to identify the factors influencing the adverse events rate of MCQT. A significant difference (P<0.05) was observed in the rates of adverse events between patients from within and outside the province where the hospital is located, patients with good and poor compliance, the type of antacids taken (rabeprazole 10 mg twice per day, rabeprazole 20 mg twice per day, esomeprazole 20 mg twice per day, vonoprazan 20 mg twice per day), and presence or absence of *H. pylori* infection symptoms at the time of screening. Further logistic regression analyses indicated that the absence of *H. pylori* infection symptoms at the time of examination, residence outside the province, and poor treatment compliance were correlated with the occurrence of adverse drug reactions. The acid-suppressant regimen of esomeprazole 20 mg twice per day correlated with the relief of adverse events (rabeprazole 10 mg twice per day) (Table 8).

Table 7 Univariate and Multivariate Analyses for Influencing Factors of Helicobacter Pylori Eradication Rates Among Patients with Rescue Therapies

Influencing Factors	Eradication Rate (%)	Univariate Analysis		Multivariate Analysis	
		$\chi 2$	*P1*	AOR	*P2*
Gender					
Male	79.71 (110/138)	0.220	0.639		
Female	81.95 (109/133)				
Age, years					
≤60	80.26 (183/228)	0.279	0.597		
>60	83.72 (36/43)				
Reasons for *H. pylori* infection screening					
Screening due to existing symptoms	73.08 (57/78)	4.226	**0.040**	0.526 (0.268~1.030)	0.061
Asymptomatic physical examination	83.94 (162/193)				
Acid suppressant regimen					
Rabeprazole 10mg twice per day	78.57 (143/182)	N/A	0.564		
Rabeprazole 20mg twice per day	84.38 (54/64)				
Esomeprazole 20mg twice per day	87.50 (21/24)				
Vonoprazan 20mg twice per day	100 (1/1)				
Adverse events		0.001	0.981		
Yes	80.70 (46/57)				
No	80.84 (173/214)				
Family history of digestive tumors					
Yes	85.71 (6/7)	N/A	1.000		
No	80.68 (213/264)				
Smoking					
Yes	73.02 (46/63)	3.217	0.073		
No	83.17 (173/208)				
Alcohol intake					
Yes	88.24 (45/51)	2.233	0.135		
No	79.09 (174/220)				
Residence					
Within	80.27 (179/223)	0.239	0.625		
Outside	83.33 (40/48)				
Compliance					
Good	84.52 (213/252)	31.939	**<0.001**	11.743 4.166~33.100)	**<0.001**
Poor	31.58 (6/19)				

Note: Categorical variables are presented as numbers; A P value in bold means <0.05.

Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

Table 8 Univariate Analyses for Influencing Factors of Adverse Events Rates Among Overall Patients

Influencing Factors	Adverse Events Rate	Univariate Analysis		Multivariate Analysis	
		$\chi 2$	*P1*	AOR	*P2*
Gender					
Male	20.47 (79/386)	1.468	0.226	–	–
Female	23.98 (106/442)				
Age, years					
≤60	23.13 (167/722)	2.014	0.156		
>60	16.98 (18/106)				

(*Continued*)

Table 8 (Continued).

Influencing Factors	Adverse Events Rate	Univariate Analysis		Multivariate Analysis	
		$\chi 2$	*P1*	AOR	*P2*
Reasons for *H. pylori* infection screening					
Screening due to existing symptoms	29.08 (82/282)	11.180	**0.001**	Reference	
Asymptomatic physical examination	18.86 (103/546)			0.576 (0.410~0.811)	**0.002**
Acid suppressant regimen					
Rabeprazole 10mg twice per day	25.04 (153/611)	N/A	**0.002**	Reference	
Rabeprazole 20mg twice per day	18.47 (29/157)			0.690 (0.441~1.080)	0.104
Esomeprazole 20mg twice per day	5.36 (3/56)			0.189 (0.058~0.617)	**0.006**
Vonoprazan 20mg twice per day	0 (0/4)			0	0.999
Family history of digestive tumors					
Yes	25.00 (7/28)	0.118	0.731		
No	22.25 (178/800)				
Smoking					
Yes	24.84 (40/161)	0.721	0.400		
No	21.74 (145/667)				
Alcohol intake					
Yes	21.94 (34/155)	0.018	0.893		
No	22.44 (151/673)				
Residence					
Within province	21.09 (147/697)	3.984	**0.046**	Reference	
Outside province	29.01 (38/131)			1.625 (1.056, 2.500)	**0.027**
Compliance					
Good	21.57 (170/788)	5.565	**0.018**	Reference	
Poor	37.50 (15/40)			2.301 (1.165, 4.543)	**0.016**

Notes: Categorical variables are presented as numbers; A P value in bold means <0.05.
Abbreviations: MLAB, minocycline-levofloxacin-antacids-bismuth regimen; MAAB, minocycline-amoxicillin-antacids-bismuth regimen; MMAB, minocycline-metronidazole-antacids-bismuth regimen.

Discussion

The present study evaluated the clinical efficacy and safety of MCQT regimens in treating *H. pylori* infection. Our analysis revealed that all three MCQT regimens (MAAB, MMAB, and MLAB regimen) achieved satisfactory *H. pylori* eradication, all as primary therapy, while MAAB and MMAB as rescue therapy. At the same time, patients who received MLAB and MAAB therapies reported fewer adverse events compared with those who received the MMAB regimen, demonstrating the safety of both regimens.

Minocycline is a semi-synthetic tetracycline derivative that binds the 30S subunit of the bacterial 70S ribosome. Minocycline interferes with peptide chain elongation, which consequently inhibits protein synthesis by the pathogens.[10] Previous studies have shown that minocycline exhibits antibacterial[11] and potent antifungal properties.[12] In 1992, Millar et al[6] revealed for the first time the anti-*H. pylori* effects of minocycline in vitro. The minimal inhibitory concentrations (MICs) of minocycline for *H. pylori* strain NCTC 11637 in modified Brucella broth is 0.25 mg/litter. To the best of our knowledge, this was the first study to illustrate the antibacterial properties of minocycline against *H. pylori*. Furthermore, minocycline has several advantages over other antibiotics. First, *H. pylori* showed a relatively lower resistance to minocycline. In 2009, a cross-section study[7] with 3521 *H. pylori* infectors in Japan showed that only 0.06% of *H. pylori* were resistant to minocycline, comparable with amoxicillin (0.03%). In 2015, a related cross-sectional study in China showed that 6.6% of clinical *H. pylori* isolates were resistant to minocycline.[8] Besides, a series of clinical trials[13–17] on minocycline-based therapies have revealed resistance ranging from 0%[16] to 9.1%.[15] These findings indicate that minocycline resistance of *H. pylori* is comparable to that of amoxicillin,[13,15,17] tetracycline,[13,15,17] Cefuroxime,[15] and lower than clarithromycin,[13,15,17] levofloxacin[13,15,17] and metronidazole.[13,15,17] Moreover, minocycline exhibits high lipophilicity and easily reaches distant tissue sites by crossing the phospholipid membranes. This pharmacological

characteristic further enhances the bioavailability and antibacterial activity of minocycline.[18,19] Of note, tetracycline is difficult to obtain in some areas and has a relatively high incidence of adverse events, which limits its application.[13,20]

In the present study, we assessed the efficacy and safety of three combinations (minocycline plus amoxicillin, minocycline plus metronidazole, and minocycline plus levofloxacin) in treating *H. pylori* infections. In China, bacterial resistance to minocycline and amoxicillin is very low.[4,15] Regimens combining two antibiotics with a low resistance rate profile are recommended for both second-line therapies and refractory *H. pylori* infection.[4] Metronidazole and levofloxacin are recommended for primary and rescue *H. pylori* treatment In China, though in combination with antibiotics with low resistance rate, either amoxicillin or tetracycline.[4] In this study, minocycline replaced amoxicillin and tetracycline due to its low resistance rate by *H. pylori*. Amoxicillin was limited in patients allergic to penicillin, while tetracycline use was limited due to its unavailability. For these reasons, combinations of minocycline plus metronidazole and minocycline plus levofloxacin might be appropriate for patients with penicillin allergy and should be explored further. In addition, it should be noted that in the present study, metronidazole was prescribed at the dosage of 1.6 g per day. Although metronidazole resistance rate by *H. pylori* was high and has been increasing in China,[4] previous studies suggested that this could be overcome by higher doses and shorter intake intervals.[3] Our previous trial in 2019 showed that RMMB (A combination of rabeprazole, metronidazole (1.6g/d), minocycline (0.2g/d), and bismuth) cleared *H, pylori* in 84.3% of the participants. Besides, no record of minocycline plus clarithromycin regimen was found in the patient data in the present study. There was no report on the efficacy of minocycline in combination with clarithromycin. To the best of our knowledge, there is no evidence of the advantages of this combination.

A few RCTs on the efficacy of MCQT against *H. pylori* have been reported. For instance, in 2019, Zhang et al[21] used a randomized controlled trial to evaluate the eradication rate and safety of minocycline-containing bismuth quadruple therapies against untreated *H. pylori* in treatment naïve patients. Findings based on the intention-to-treat (ITT) analysis revealed the eradication rates of RMAB (in combination with rabeprazole, minocycline, amoxicillin, and bismuth) and RMMB (in combination with rabeprazole, minocycline, metronidazole, and bismuth) were 85.7% and 77.1% respectively. Both were prior to the control (rabeprazole, amoxicillin, clarithromycin, and bismuth regimen, 71.7%) with significant differences ($P<0.05$). A total of 30.0% and 37.5% of patients in RMAB and RMMB groups, respectively, reported the occurrence of adverse events, both prior to that of the control group (40.0%). A related RCT by Suo et al[13] showed that the eradication efficacy of MCQT when used as the first-line regimen was comparable to that of tetracycline-containing quadruple therapy (TCQT). At the same time, the safety and compliance of MCQT were similar to those of TCQT. A meta-analysis of five RCTs evaluated the efficacy and safety of MCQT against *H. pylori* infection.[9] The results showed that the eradication rate (83.8%) and the occurrence of adverse effect rate (35.9%) were comparable to those of the control group. Based on these results, the authors cautioned that the results should be treated with caution because adequate subgroup analyses, especially analyses of primary and rescue therapies, were not performed owing to the limited number of included trials. In summary, based on the previous RCTs, evidence supporting MCQT is limited, with some of the results being inconsistent. In comparison, the present study retrospectively evaluated the efficacy and safety of multiple MCQT regimens as primary and rescue therapies for *H. pylori* infection based on a relatively larger sample size, which strengthened the evidence provided by previous RCTs, confirming the efficacy and safety of MCQT in treating *H. pylori* infections. Moreover, to our knowledge, this is the first report on the efficacy and safety of the MLAB regimen in treating *H. pylori* infection. Our results showed that the MLAB regimen is effective as primary therapy but not as a rescue therapy.

Our findings showed that MAAB, MMAB, and MLAB regimens yielded a satisfactory *H. pylori* eradication rate (80%) when used as a primary therapy, consistent with previous RCTs.[9,13] The high *H. pylori* eradication by MAAB, MMAB, and MLAB may be related to the relatively low rate of primary resistance to minocycline by bacteria. A lower eradication rate and higher adverse event rate were identified in the MMAB group, which implies that adverse events and poor compliance might play an important role in reducing the eradication efficacy of antibiotics.

Among rescue therapies, the MAAB regimen had the highest eradication rate (86.27%), possibly because the MAAB regimen (ie, amoxicillin and minocycline) has low resistance rates in China.[8] Similarly, MMAB and MLAB regimens demonstrated lower eradication rates than MAAB because metronidazole and levofloxacin, which are some of the components contained in the MMAB and MLAB regimens, had high resistance rates in China.[8] In summary, the

differences in eradication rates among MAAB, MMAB, and MLAB could be attributed to resistance development to these antibiotics. Moreover, significantly different eradication rates were observed between MMAB and MLAB regimens. One explanation for the failed eradication of *H. pylori* in rescue therapies could be primary and secondary resistance to the antibiotics.[5,22] Although the previous treatments the patients had received and the status of antibiotic resistance among the included patients were unclear, it is reasonable to speculate that the differences in antibiotic resistance rates contributed to the above-mentioned differences in eradication rates. Second, the sample size of the MLAB regimen group as rescue therapy was relatively small.

The present study also found the occurrence of adverse events in patients who received MCQTs. Across all the included patients, the most common adverse event was dizziness (9.06%) followed by abdominal discomfort (6.04%), diarrhea (4.83%), and nausea (4.59%), consistent with previous studies.[9] Minocycline, a semi-synthetic tetracycline, shares similar side effects with tetracycline. Compared with tetracycline, minocycline is more frequently accompanied by reversible vestibular reactions, including nausea, vomiting, dizziness, and motor disorders. Therefore, we speculated that the adverse events mentioned above might be related to the usage of minocycline.[23] The highest incidence of adverse events (51.43%) was reported in patients on the MMAB regimen. Metronidazole treatment may cause multiple side effects, including gastrointestinal symptoms (nausea and/or vomiting, abdominal pain, and diarrhea),[13,24] which were similar to those induced by minocycline. Accordingly, we speculated that such frequently occurring adverse events might be caused by the combination of minocycline and metronidazole. For example, in 2023, Suo et al[13] conducted an RCT to compare the efficacy and safety of metronidazole-containing quadruple therapy (MeCQT) and tetracycline-containing quadruple therapy (TCQT). Patients in both groups reported the same adverse events of dizziness, nausea, diarrhea, abdominal pain, and abdominal discomfort. However, the incidence of dizziness in the MeCQT group was significantly higher than in the TCQT group. These results demonstrate that metronidazole and tetracycline treatment shared similar side effects in *H. pylori* patients. Accordingly, adverse events are likely to occur in a combination therapy of minocycline (or other tetracyclines semi-synthetic tetracyclines) and metronidazole in treating *H. pylori* infection. In addition, high metronidazole resistance by -*H. pylori* has been reported in China.[25] In this study, 400 mg of metronidazole was taken four times per day, which is the maximum safe range dose recommended in clinical use, and this may have contributed to the development of adverse events as well.

The factors influencing the efficacy and safety of MCQT therapy were also explored in this study. Poor compliance was associated with failed *H. pylori* eradication, suggesting that better compliance should be encouraged to increase eradication rates. Patients who received stronger antacids (eg, vonoprazan or esomeprazole) reported fewer adverse reactions, indicating that stronger antiacid therapy reduces the occurrence of adverse events in patients on MCQT therapy. Besides, asymptomatic patients who underwent *H. pylori* screening reported more adverse events. This might have been caused by several reasons. On one hand, asymptomatic patients might easily notice the newly developed discomforts occurring during treatment as side effects of the treatment. On the other hand, some of the side effects of eradication therapy, such as nausea, vomiting, etc., are similar to those of *H. pylori* infection. Accordingly, it is difficult to distinguish such symptoms from drug-related side effects, especially for patients who had these symptoms before initiation of treatment. This, the differences in the occurrence of side effects might have been affected by reporting bias.

This study had some limitations. First, the present study was retrospective, and it was not possible to obtain certain data with accuracy during the treatment period owing to recall and reporting bias. In fact, we could not grade the severity of the adverse events, which, to some extent, limited the safety assessment. Second, the cytochrome P4502C19 (CYP2C19) profile and antibiotic susceptibility of the included patients were unclear. Thus, we could not accurately evaluate the efficacy of MCQT based on the status of antibiotic resistance. Finally, the sample size was not large enough; hence, the efficacy of certain MCQT regimens could not be determined with high accuracy.

Conclusion

The present study provides evidence for the efficacy and safety of MCQT in treating *H. pylori* infection. MCQT regimens have demonstrated satisfactory efficacy and safety as primary and rescue therapies for *H. pylori* infection. More prospective studies with larger sample sizes and needed to provide more comprehensive clinical data on the efficacy and safety of MCQT.

Data Sharing Statement

All data and materials generated during the current study can be availed by the correspondence author upon reasonable request.

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Disclosure

The authors declare that this research was conducted without any commercial or financial relationships that could be construed as potential conflicts of interest.

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