ORIGINAL ARTICLE

Bismuth, lansoprazole, amoxicillin and metronidazole or clarithromycin as first-line *Helicobacter pylori* therapy

Wei Zhang,[1,2] Qi Chen,[1,2] Xiao Liang,[1,2] Wenzhong Liu,[1,2] Shudong Xiao,[1,2] David Y Graham,[3] Hong Lu[1,2]

[1]GI Division, Renji Hospital, School of Medicine, Shanghai Jiao-Tong University, Shanghai Institution of Digestive Disease, Shanghai, China
[2]Key Laboratory of Gastroenterology & Hepatology, Ministry of Health, Shanghai, China
[3]Michael E. DeBakey VA Medical Center, and Baylor College of Medicine Houston, Houston, Texas, USA

Correspondence to
Dr Hong Lu, Key Laboratory of Gastroenterology & Hepatology, Ministry of Health, 145 Middle Shandong Rd, Shanghai 200001, China; hlu@sjtu.edu.cn

ABSTRACT

Objective To evaluate the efficacy and tolerability of replacing tetracycline with amoxicillin in bismuth quadruple therapy.

Design Subjects who were infected with *Helicobacter pylori* and naïve to treatment were randomly (1:1) assigned to receive a 14-day modified bismuth quadruple therapy: lansoprazole 30 mg, amoxicillin 1 g, bismuth potassium citrate 220 mg (elemental bismuth), twice a day with metronidazole 400 mg four times a day (metronidazole group) or clarithromycin 500 mg twice a day (clarithromycin group). Six weeks after treatment, *H. pylori* eradication was assessed by ^{13}C-urea breath test. Antimicrobial susceptibility was assessed by the twofold agar dilution method. This was a non-inferiority trial.

Results Two hundred and fifteen subjects were randomised. Metronidazole and clarithromycin containing regimens achieved high cure rates: 94 of 97 (96.9%, 95% CI 93.5% to 100%) and 93 of 98 (94.9%, 95% CI 90.5% to 99.3%) by per-protocol and 88.9% (95% CI 83.0% to 94.8%) and 88.8% (95% CI 82.8% to 94.8%) by intention-to-treat, respectively. Amoxicillin, metronidazole and clarithromycin resistance rates were 1.5%, 45.5% and 26.5%, respectively. Only clarithromycin resistance reduced treatment success (eg, susceptible 98.6%, resistant 76.9%, p=0.001). Adverse events were more common in the metronidazole group.

Conclusions These results suggest that amoxicillin can substitute for tetracycline in modified 14 day bismuth quadruple therapy as first-line treatment and still overcome metronidazole resistance in areas with high prevalence of metronidazole and clarithromycin resistance. Using clarithromycin instead of metronidazole was only effective in the presence of susceptible strains.

Trial registration number NCT02175901.

Significance of this study

What is already known on this subject?
▶ *Helicobacter pylori* therapies including standard triple therapy no longer reliably achieve acceptable *H. pylori* eradication rates because of increasing antimicrobial resistance.
▶ Metronidazole resistance can be overcome with traditional bismuth quadruple therapy when given at full dose for 14 days.
▶ Bismuth quadruple therapy has long been used successfully; it has never become widely used in part because of the relatively high incidence of side effects and because in recent years tetracycline has been largely unavailable.
▶ Studies without concomitant susceptibility testing may result in misleading conclusions.

What are the new findings?
▶ Amoxicillin can substitute for tetracycline in bismuth quadruple therapy and still overcome metronidazole resistance (eg, cure rates were 96.4% vs 93.3%) for metronidazole susceptible versus resistant infections.
▶ A high overall cure rate with the proton pump inhibitor, bismuth, amoxicillin and clarithromycin combination did not reflect an improved cure rate with clarithromycin-resistant strains (eg, 98.6% vs 76.9% for clarithromycin susceptible vs resistant infections).

How might it impact on clinical practice in the foreseeable future?
▶ This 14-day non-tetracycline-containing bismuth quadruple therapy in which amoxicillin replaced tetracycline is the first new regimen in decades that was able to overcome resistance to a key ingredient (ie, metronidazole) and is thus potentially a new first-line therapy.

INTRODUCTION

Triple therapy including a proton pump inhibitor (PPI), amoxicillin and clarithromycin are no longer recommended as empirical first-line therapy to treat *Helicobacter pylori* infections except in areas where clarithromycin resistance is still low.[1 2] Worldwide the resistance rate to clarithromycin has increased because of the widespread use of macrolides.[3–5] Recent guidelines suggest classic bismuth-containing quadruple therapy (PPI-bismuth-metronidazole-tetracycline) as an alternative so that effectiveness is not influenced by clarithromycin resistance and

metronidazole resistance and resistance can be at least partially overcome with full dose therapy especially when given for 10 days or preferably 14 days.[1 6–8] However, poor adherence has been a problem especially when full doses of tetracycline and metronidazole are given.

Metronidazole is a major antibiotic used to treat *H. pylori* infection but increasing resistance has

limited its usefulness. The combination of amoxicillin and metronidazole-containing bismuth therapy has not been widely used in clinical practice. Studies done almost 20 years ago suggested it was less effective than clarithromycin-based triple therapy, but that study was based on a clinical trial using ranitidine bismuth citrate.[9] PPI, amoxicillin and metronidazole triple therapy also has a long history, is dose and duration susceptible, and is approved as alternate therapy in Japan.[10 11] However, it is rendered ineffective by the presence of metronidazole resistance.[10] A study of omeprazole 20 mg, amoxicillin 1 g as a substitute for tetracycline, tinidazole 500 mg and bismuth subcitrate 240 mg (elemental bismuth) given every 12 h for only 7 days achieved a per-protocol (PP) cure rate of 86% and intention to treat (ITT) of 84.1%.[12] That study was never followed up with another study of longer duration and as no susceptibility testing was done the effect of resistance cannot be assessed.

The aim of the present study was to evaluate the efficacy and tolerability of 14-day modified bismuth quadruple therapy in which tetracycline was replaced by amoxicillin. The comparator was this regimen where metronidazole was replaced by clarithromycin. We used full dose metronidazole (ie, 1600 mg) because prior studies have suggested that to overcome metronidazole resistance doses of 1500 mg to 1600 mg were required.[13 14] Susceptibility testing was performed to investigate the effect of resistance on the results of treatment.

MATERIALS AND METHODS
Subjects and study design
This was a randomised single-centre non-inferiority open-label study of modified bismuth quadruple therapy in which bismuth was given twice a day and amoxicillin replaced tetracycline. The fourth drug was metronidazole 400 mg four times a day or clarithromycin 500 mg twice a day. Between July 2014 and December 2014, consecutive subjects who presented with epigastric symptoms had endoscopically proven functional dyspepsia or scarred peptic ulcers were considered for recruitment in this study. H. pylori infection was diagnosed by positive rapid urease test and ^{13}C-urea breath test (UBT) or anti-H. pylori antibody. Exclusion criteria included subjects less than 18 years old, with history of H. pylori infection treatment, with previous gastric surgery, pregnancy, lactation, major systemic diseases, administration of antibiotics, bismuth, antisecretory drugs in the preceding 8 weeks or allergy to any one of the given medication in the regimens.

Randomisation and blinding
Eligible subjects were assigned to two groups using a computer-generated code with random, permuted blocks, either receiving metronidazole group therapy or clarithromycin group therapy.

All randomisation codes were put into sealed opaque envelopes and kept by an independent research assistant. After obtaining informed consent, the investigators would call the independent research assistant to open the envelope for the allocated regimen for that subject.

Blinding: This was an open-label study. Urea breath test personnel were unaware of the treatment given.

Interventions
Eligible subjects received one of the two different schemes for 2 weeks: lansoprazole (Takeda Pharmaceutical Company, Osaka, Japan) 30 mg twice a day, bismuth potassium citrate (Livzon Pharmaceutical Group, Zhuhai, China) 300 mg (220 mg elemental bismuth) twice a day, amoxicillin (Zhuhai United Laboratories, Zhuhai, China) 1000 mg twice a day and metronidazole (Shanghai Xinyi Wanxiang Pharmaceutical Industry Company, Shanghai, China) 400 mg four times a day, (metronidazole group) or clarithromycin (Livzon Pharmaceutical Group, Zhuhai, China) 500 mg twice a day (clarithromycin group).

In this study PPI and bismuth were given before meals and antibiotics were given 30 min after meals. Six weeks after completion of therapy, eradication was defined as negative result from UBT (<4‰) (4‰ as the cut-off values).

All subjects were educated about the drug administration time, possible adverse events and how to report adverse reaction. During the treatment period, the subjects kept a diary to monitor compliance and symptoms. Side effects were scored as mild, moderate or severe according to their influence on daily activities. Compliance was defined as good when they had taken more than 80% of the total medication.

H. pylori strains
One biopsy specimen was collected from the gastric antrum or corpus to isolate H. pylori. The biopsy specimens were cultured and maintained on brain heart infusion agar medium (OXOID, Basingstoke, UK) containing 5% defibrinated sheep blood under microaerophilic conditions (85% N_2, 10% CO_2, 5% O_2) at 37°C. We stored all isolates in a brain heart infusion broth (Difco Laboratory, Detroit, Michigan, USA) supplemented with 30% glycerol at −80°C. Clinical isolates were identified as H. pylori if found positive for urease, oxidase, catalase and Giemsa staining.

Agar dilution and minimal inhibitory concentrations
Minimal inhibitory concentrations of metronidazole, clarithromycin and amoxicillin were determined by the twofold agar dilution method. H. pylori was suspended in saline and measured using spectrophotometer. The bacterial suspensions (10^8 colony forming units per millilitre) were then plated with an inoculator (Sakuma Seisaku, Tokyo, Japan) onto agar plates containing various concentrations of the abovementioned antibiotics. After 3 days of microaerophilic incubation, minimal inhibitory concentration was defined as the lowest drug concentration that prevented visible growth of bacteria. ATCC43504 was used as the quality control strain. The resistance break points for amoxicillin, clarithromycin and metronidazole were defined as >0.5 μg/mL, 2 μg/mL and 8 μg/mL, respectively.

Sample size estimation and statistical analysis
According to previous trials, eradication rates were 93%[15] and 90.6%[16] in similar regimens when used as first-line treatment. Assuming an average eradication rate of 91%, an α-error of 0.05, a β-error of 0.20 and equivalence margin of −10%, at least 202 participants (101 subjects in each group) would be required in the non-inferiority trial.

Comparative non-inferiority of the two groups was assessed through hypothesis testing (one-sided μ test) and derivation of two-sided 95% CIs. The eradication rates were evaluated by ITT and PP analyses. A modified ITT (MITT) analysis (which is the outcome of all who received a dose and for whom an outcome measure is available) was also done.[17] Subgroup analyses were also performed based on the results of agar dilution.

Between-group differences were evaluated using Student's t test for continuous variables and Pearson's χ^2 test for categorical variables. The significance level was set at p<0.05.

RESULTS

Two quadruple therapies were given to 215 *H. pylori* positive subjects referred to our centre for gastroscopy. Table 1 gave the demographic and clinical characteristics of the subjects. Flow of screening and recruitment of study subjects was shown in figure 1. There was no significant difference between the two groups in terms of sex, age, smoking or antibiotics resistance. The prevalence of peptic ulcer disease was also similar in the two groups.

H. pylori eradication rates

In the PP analysis, the lower bound of the 95% CI for difference between metronidazole and clarithromycin groups was greater than the pre-established non-inferiority margin of –10% (95% CI –2.7% to 6.7%, p<0.0001). The same CI was derived with the ITT population (table 2).

PP and ITT *H. pylori* eradication rates were 96.9% (94/97; 95% CI 93.5% to 100%) and 88.9% (96/108; 95% CI 83.0% to 94.8%) for the metronidazole group and 94.9% (93/98; 95% CI 90.5% to 99.3%) and 88.8% (95/107; 95% CI 82.8% to 94.8%) for the clarithromycin group, respectively. In the MITT analysis, the eradication rate was 91.4 (96/105; 95% CI 86.1% to 96.8%) with two of eight subjects of low compliance and negative UBT results in the metronidazole group, and 91.3% (95/104; 95% CI 85.9% to 96.7%) with two of six subjects of low compliance and negative UBT results in the clarithromycin group.

Susceptibility testing

Two hundred strains were successfully cultured and recovered from 215 subjects. The resistance rate of *H. pylori* to amoxicillin was 1.5% (3/200), metronidazole 45.5% (91/200) and clarithromycin 26.5% (53/200).

Subgroup analysis was also performed to determine the effect of clarithromycin and metronidazole resistance on eradication rates (table 3). The eradication rates were similar with the metronidazole-containing regimen with metronidazole susceptible and resistant strains (susceptible 96.4%, 54/56, and resistant 93.3%, 42/45) (p=0.802). In contrast, eradication rates with the clarithromycin susceptible strains in the clarithromycin-containing regimen were significantly greater (98.6% (72/73) with susceptible strains compared with resistant strains 76.9% (20/26)) (p=0.001) (figure 2).

Compliance and side effects

Three subjects in each group were lost to follow-up and no outcome data was available and they were scored as treatment
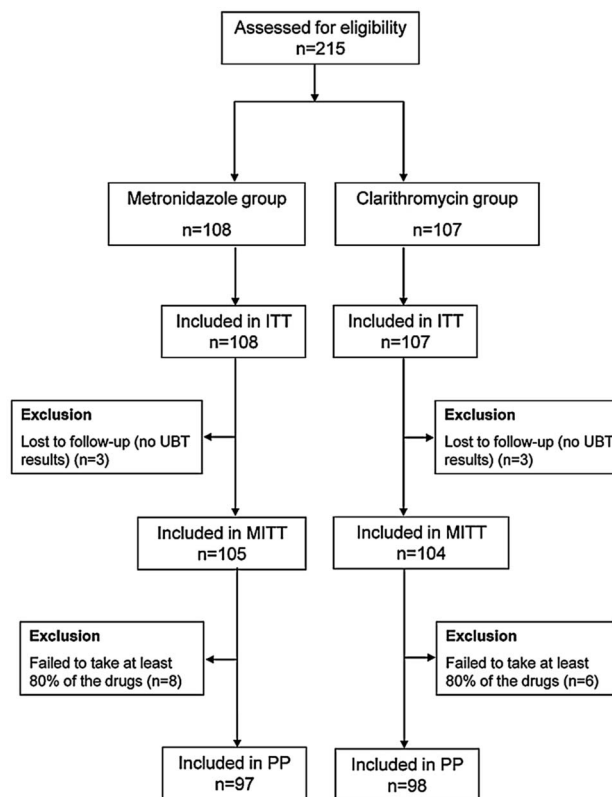

Figure 1 Flow of screening and recruitment of study subjects. ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol; UBT, urea breath test.

failure of the primary ITT analysis. Eight subjects in the metronidazole group and six subjects in the clarithromycin group failed to take at least 80% of the drugs due to adverse effects, including three subjects of each group that were withdrawn from the treatment because of nausea, drowsiness and skin allergy, but they received UBT testing post treatment. Both regimens were well tolerated (92.6% vs 94.4%, p=0.593). Side effects were reported by 21.3% (23/108) in the metronidazole group vs 11.2% (12/107) in the clarithromycin group (p=0.045). Side effects included nausea, fatigue, bad taste, epigastric pain, skin rash, diarrhoea, dizziness and fever. They all disappeared after cessation of medications. Side effects were significantly more frequent in the metronidazole group than in the clarithromycin group (p=0.045). Nausea was the most frequent adverse event in the metronidazole group (p=0.031) (table 4).

Table 1 Demographic and clinical data of subjects

Variables	Metronidazole group	Clarithromycin group
Number of subjects	108	107
Gender (male/female)	48/60	56/51
Age, years (range)	44.6 (22–77)	44.1 (18–79)
Diagnosis		
Functional dyspepsia	88	78
Peptic ulcer	20	29
Metronidazole resistance, n (%)	45 (44.6%)	46 (46.5%)
Clarithromycin resistance, n (%)	27 (26.7%)	26 (26.3%)
Dropout	3	3
Compliance (taken>80% of tablets)	92.6% (100/108)	94.4% (101/107)

Table 2 Eradication rate of each group

Analysis	Metronidazole group	Clarithromycin group	95% CI for difference between metronidazole and clarithromycin groups	p Value
ITT	88.9% (96/108)	88.8% (95/107)	–7% to 7.2%	<0.0001
95% CI	83.0% to 94.8%	82.8% to 94.8%		
PP	96.9% (94/97)	94.9% (93/98)	–2.7% to 6.7%	<0.0001
95% CI	93.5% to 100%	90.5% to 99.3%		
MITT	91.4% (96/105)	91.3% (95/104)	–6.3% to 6.5%	<0.0001
95% CI	86.1% to 96.8%	85.9% to 96.7%		

ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.

Table 3 Effect of CLA and MET resistance on *H. pylori* eradication rates in the MITT population

MITT population	MET group Successful, n/N (%)	CLA group Successful, n/N (%)
Cultured	101	99
MET-S, CLA-S	39/40 (97.5%)	38/39 (97.4%)
MET-R, CLA-S	32/34 (94.1%)	34/34 (100%)
MET-S, CLA-R	15/16 (93.7%)	10/14 (71.4%)
MET-R, CLA-R	10/11 (90.9%)	10/12 (83.3%)

CLA, clarithromycin; MET, metronidazole; MITT, modified intention-to-treat; R, resistant; S, susceptible.

Table 4 Adverse events in the treatment groups

Variables	Metronidazole group	Clarithromycin group	p Value
Nausea	9	2	0.031
Fatigue	3	0	0.248
Bad taste	1	3	0.607
Epigastric pain	2	2	1.0
Skin rash	3	3	1.0
Diarrhoea	1	2	0.993
Dizziness	3	0	0.248
Fever (>37.5°C)	1	0	0.240
Total subjects, % (n)	21.3% (23)	11.2% (12)	0.045

DISCUSSION

Susceptibility testing for *H. pylori* infections is generally unavailable forcing clinicians to choose an antibiotic regimen empirically. Empirical choice of an effective regimen has become increasingly difficult because resistance to commonly used antibiotics has increased worldwide. In most countries amoxicillin and tetracycline resistance in *H. pylori* is still rare. Among the remaining commonly used antibiotics, clarithromycin, fluoroquinolones, metronidazole, only metronidazole resistance can be partially overcome by increasing the dose and duration of therapy.[10 14 18] However, that statement is generally only true for bismuth quadruple therapy. The widespread unavailability of tetracycline coupled with the fact that many countries still forbid bismuth for therapy has made worldwide acceptance of this regimen slow. In addition, the regimen seems less effective in some countries such as Turkey and Iran possibly because of the presence of tetracycline resistance.[19–21] Finally, the combination of metronidazole and tetracycline often results in significant side effects. Here we asked whether one could replace tetracycline with amoxicillin or clarithromycin and still achieve an effective regimen.

The resistance rates of *H. pylori* to amoxicillin, metronidazole and clarithromycin were 1.5%, 45.5% and 26.5% in our study. Our results suggest that it may be possible to replace tetracycline with amoxicillin and provide effective therapy as in susceptible strains cure rates exceeded 90%. We were also largely able to

overcome metronidazole resistance with 1600 mg of metronidazole as the cure rate with metronidazole resistant strains was essentially identical to that with susceptible strains (eg, 93.3% vs 96.4% on MITT analysis). One advantage of our study is the use of agar dilution to assess metronidazole resistance as the E-test tends to overestimate the prevalence of resistance and thus the effectiveness in the presence of resistance. Importantly, the side effects remained higher (21.3%) than one would wish. Some subjects despite poor compliance had negative UBT results demonstrating the importance of follow-up testing in all subjects and suggesting that subsequent studies should possibly evaluate different durations, doses or dosing intervals of metronidazole with the goal of identifying the optimum regimen that will reliably cure *H. pylori* despite metronidazole resistance.

The alternate therapy replaced metronidazole with clarithromycin and provided data without metronidazole and in relation to resistance. A previous study with this regimen was highly successful.[15] In that study clarithromycin resistance was 18%. In this study clarithromycin resistance had increased to 26.5%. Although the overall eradication rates were acceptable (ie, 88.8% ITT and 94.9% PP), clarithromycin resistance significantly hampered treatment success (eg, 98.6% with susceptible strains vs 76.9% with resistant strains, p=0.001). Thus while the overall results were acceptable, those with clarithromycin resistant infections received relatively ineffective therapy suggesting that this clarithromycin-containing therapy should not be used empirically, because approximately a quarter of the subjects would receive inadequate therapy. This study illustrates how studies not accompanied by susceptibility testing can result in misleading conclusions regarding effectiveness. Finally, the fact that clarithromycin resistance adversely affected outcome confirmed that the beneficial effect was not entirely explained by the effectiveness of the amoxicillin-PPI dual therapy component in an Asian population.[22]

In the era of increasing antibiotic resistance, 'use what works best locally' is probably the best advice for clinicians to choose treatment for *H. pylori*. The combination and dose of amoxicillin and metronidazole was strategically selected because it was likely to be useful in areas of high antibiotic resistance. Compared with the previous study which used 1 g tinidazole per day for only 7 days, we used a high dose of metronidazole (1.6 g/day) for 14 days and achieved a PP cure rate of 96.9% despite a high prevalence of metronidazole resistance. The prior study achieved 86% in an area with lower prevalence to metronidazole resistance.[12] A 10-day triple therapy using high dose of amoxicillin (3 g/day) and metronidazole (1.5 g/day) achieved an 88.2% PP eradication rate, however, since metronidazole resistance was not evaluated and it was a triple therapy, the results
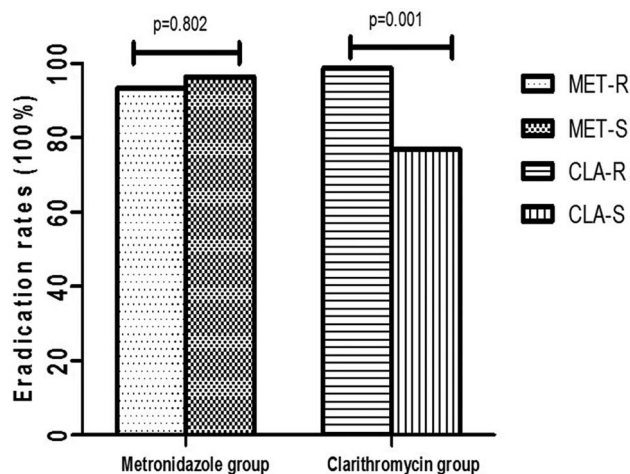

Figure 2 Effect of clarithromycin and metronidazole resistance on *H. pylori* eradication rates. MET, metronidazole; CLA, clarithromycin; S, susceptible; R, resistant.

are difficult to compare with ours.[23] Our data with clarithromycin in this study and fluoroquinolones in another study[24] suggested that adding bismuth and prolonging treatment duration likely resulted in improved efficacy. In fact, our amoxicillin-containing modified bismuth quadruple therapy proved to be clearly superior to the results of the 10-day standard triple therapy in China (eg, 73% PP cure rate) or sequential therapy (eg, 76% PP cure rate) as reported in a recent multicentre study by Zhou et al[25] Our excellent results with resistant strains suggest it is a good choice for first-line treatment.

Bismuth salts may play an important role in bismuth-containing quadruple therapy. Bismuth is a topical antimicrobial to which resistance does not develop. Different preparations contain different amounts of elemental bismuth. For our study we used bismuth potassium citrate, containing 110 mg elemental bismuth per 300 mg capsule, with two capsules given twice a day. Our results need to be compared using other bismuth preparations, such as bismuth subsalicylate and colloidal bismuth subcitrate.

Antibiotic resistance and compliance are the important factors influencing eradication result. In order to make the regimens more acceptable, we provided a card for participants, which showed the drug administration time (eg, PPI and bismuth were given before meals and antibiotics were given 30 min after meals) and provided specific explanation regarding the goals of treatment, the possible adverse events (eg, abdominal pain, nausea, diarrhoea and black stools) and the necessity to complete the full course. The adherence to both regimens was excellent (92.6% vs 94.4%, p=0.593). Our results are consistent with the notion that pretreatment counselling is very important for good success in H. pylori eradication.[26 27]

Our study has some limitations. The subpopulations with clarithromycin resistance, metronidazole resistance and dual resistance were numerically relatively small (ie, only 11 with dual resistance in metronidazole group, table 3). Estimation of eradication rates in these small subpopulations of resistant subjects is therefore susceptible to the effect of random error and may achieve a less reliable conclusion regarding the actual outcome in the presence of resistance. Effectiveness of therapy should also be determined in relation to the level of metronidazole resistance although, to date, the level of resistance has not proven to relate to differences in effectiveness.[7 28]

In summary, this study demonstrated that a modified bismuth-containing quadruple therapy in which tetracycline was replaced by amoxicillin achieved an excellent eradication rate, irrespective of metronidazole resistance. However, despite removal of tetracycline and use of bismuth twice a day, side effects remained high in the metronidazole therapy group; nausea was the most frequent adverse event. Under these circumstances, empirical treatment with the high-dose metronidazole-containing modified bismuth quadruple therapy, especially in regions with high prevalence of antibiotic resistance or where antimicrobial susceptibility testing is not available, would potentially achieve high success rates.

Contributors HL: study concept and design, acquisition of data, data interpretation and drafting of the manuscript. WZ: patient recruitment, acquisition of data, statistical analysis and critical revision of the manuscript. QC and XL: patient recruitment and study coordination. WL and SX: study supervision and technical support. DYG: study supervision and critical revision of the manuscript.

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Wei Zhang, Qi Chen, Xiao Liang, Wenzhong Liu, Shudong Xiao, David Y Graham and Hong Lu

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