Efficacy of quadruple therapy with clarithromycin based on faecal molecular antimicrobial susceptibility tests as first-line treatment for Helicobacter pylori infection: a protocol of a single-centre, single-blind, randomised clinical trial in China

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ABSTRACT

Introduction Helicobacter pylori is the most well-known risk factor for gastric cancer. Antibiotic resistance is the main reason for the failure of H. pylori eradication, and understanding the antibiotic resistance before treatment may be the main determinant of successful eradication of H. pylori. This study aims to evaluate the efficacy and safety of quadruple therapy based on faecal molecular antimicrobial susceptibility tests for the first-line eradication of H. pylori infection.

Methods and analysis This is a single-centre, single-blind, randomised controlled trial, enrolling 855 patients with H. pylori infection. Patients are randomised to three groups for a 14-day treatment: group A: amoxicillin–clarithromycin-based bismuth-containing quadruple therapy (BOT) (rabeprazole 10 mg, amoxicillin 1 g, clarithromycin 500 mg and colloidal bismuth 200 mg two times per day); group B: clarithromycin medication history-based BOT (rabeprazole 10 mg, amoxicillin 1 g, furazolidone 100 mg (with clarithromycin medication history)/clarithromycin 500 mg (without clarithromycin medication history) and colloidal bismuth 200 mg two times per day); group C: antimicrobial susceptibility test-based BOT (rabeprazole 10 mg, amoxicillin 1 g, clarithromycin 500 mg (clarithromycin-sensitive)/furazolidone 100 mg (clarithromycin resistant) and colloidal bismuth 200 mg two times per day). The primary end point is the eradication rate. The secondary end points are the incidence of adverse events and compliance.

Ethics and dissemination This study was approved by the Ethics Committee of Second Affiliated Hospital, School of Medicine, Zhejiang University (Number 20230103). The results will be published in the appropriate peer-reviewed journal.

Trial registration number NCT05718609.

INTRODUCTION

Helicobacter pylori was listed as a Class I carcinogen by the World Health Organization in 1994 and is closely associated with a variety of digestive tract diseases, such as chronic gastritis, peptic ulcer, gastric cancer and mucosa-assisted lymphoid tissue (MALT) lymphoma. About 90% of non-cardia gastric cancer is associated with H. pylori infection and the eradication of H. pylori makes intestinal gastric cancer a preventable disease.

Amoxicillin–clarithromycin-containing bismuth-containing quadruple therapy (BQT) is one of the most useful regimens against H. pylori. Though the eradication rate of amoxicillin-based and clarithromycin-based BQT is over 85% according to our previous study, the resistance to clarithromycin has been increasing in recent years and is considered a major cause of the failure of clarithromycin-based therapy. According to a systematic review and meta-analysis in...
2017, the prevalence of resistance to clarithromycin has risen significantly over time in the Asia-Pacific region in the past two decades, and the clarithromycin-containing regimens should be avoided in countries where the prevalence of clarithromycin resistance is higher than 20%. While the eradication rate for susceptibility-guided therapy with clarithromycin is quite promising, at >95%. Success of first-line eradication is likely to inhibit further bacterial resistance, decrease the difficulty of retreatment and reduce the medical burden, so it is better to eradicate *H. pylori* successfully at the initial treatment.

Nevertheless, because of the invasive examination to sampling, the economy–benefit ratio and the harsh cultivation conditions, traditional antimicrobial susceptibility test is rarely used before first-line eradication treatment in the real world. Molecular biology methods mainly used for the detection of clarithromycin-resistant genotypes of *H. pylori* have important guiding value for *H. pylori* eradication therapy.

Clarithromycin resistance is usually due to the mutation of A2142C/G and A2143G in H. pylori’s 23S ribosomal subunit RNA, which makes it possible to detect the resistance to clarithromycin using PCR kits or sequencing methods detecting 23S ribosomal RNA point mutations. In recent years, molecular assays for the detection of genotypic antibiotic resistance markers of *H. pylori* have been described, with many requiring endoscopically collected tissues and a few using non-invasively collected samples, which showed similar detection accuracy. Traditional molecular antimicrobial susceptibility tests via PCR-based assays directly from gastric mucosal tissues successfully bypass the need for culture but still require invasive collection methods. Compared with that, faecal antimicrobial susceptibility tests can inform and guide treatment choices by providing baseline antibiotic resistance status via antibiotic-associated single nucleotide polymorphisms (SNPs) in a rapid, accurate manner from non-invasively collected stool specimens, thus successfully obviating the need for endoscopy. Previous studies showed that molecular test using PCR kits in stool samples has good analytical sensitivity for the detection of clarithromycin-resistant *H. pylori*, with about 95% categorical agreement compared with agar dilution using *H. pylori* isolated from biopsy specimens. According to Zhou and Song’s study, the suitability of widespread use of first-line eradication therapy based on drug-sensitive results requires the eradication efficacy, efficiency–cost ratio, safety and the feasibility in clinical practice. More convenient, much safer and relatively non-expensive methods of sampling make it possible to popularise the antimicrobial susceptibility tests catering to both initial and salvage treatments.

What is more, the resistance to clarithromycin is also related to the medication history. Thus, to elevate the eradication rate and avoid multiple treatments, the eradication regimen tailored by knowledge of antibiotic medication history is recommended in the empiric eradication of *H. pylori* infection. *H. pylori* remains highly sensitive to amoxicillin, furazolidone and tetracycline in China, especially East China. Antibiotic regimens with amoxicillin and furazolidone dominated in the past few years, as tetracycline was not available in our hospital pharmacy. Again, we choose furazolidone as an alternative to clarithromycin in this study. A meta-analysis stated that a 14-day furazolidone-containing regimen with a low daily dose of 200 mg was well tolerated and should be used as first-line treatment. Though Federal Drug Agency warns that furazolidone may reduce fertility or injure unborn children, the International Agency for Research on Cancer classified furazolidone into group 3, that is, not carcinogenic in humans. No serious adverse events (AEs) were reported among the cases in our previous large-scale retrospective study containing 25 796 patients. Furazolidone-containing therapies with a high eradication rate should be re-evaluated in other countries.

This essay described a protocol aimed to explore the efficacy, safety and economic benefits of the first-line therapy for *H. pylori* guided by faecal antimicrobial susceptibility tests. Our study might provide new evidence to inform the value of faecal antimicrobial susceptibility tests in first-line treatment to help to reduce therapeutic failure and the subsequent need for additional therapy courses, which in turn could result in decreased compliance, increased potential side effects and increased medical economic burden.

**METHODS AND ANALYSIS**

We developed this protocol according to the Standard Protocol Items: Recommendations for Interventional Trials. The trial is registered at ClinicalTrials.gov and any important changes to the protocol will be implemented there.

**Objectives**

This trial aims to explore the clinical value of clarithromycin-contained quadruple therapy based on faecal molecular antimicrobial susceptibility tests as the first-line treatment for *H. pylori* infection to improve the eradication rate.

**Trial design and setting**

This study is designed as a single-centred, single-blind, randomised trial. Group A will be treated with amoxicillin-based and clarithromycin-based BQT; group B and group C will be treated with amoxicillin-based and clarithromycin-based BQT or amoxicillin-based and furazolidone-based BQT according to the history of clarithromycin medication and the results of faecal antimicrobial susceptibility tests, respectively. This study will be conducted in the Department of Gastroenterology of Second Affiliated Hospital, School of Medicine, Zhejiang University (SAHZU) in China. The start of the recruitment is planned in March 2023 and should be completed within the following 1 year.
Participant selection

Inclusion criteria

Participants enrolled should meet the following criteria: (1) participants aged 18–65 with no history of eradication treatment; (2) diagnosed as *H. pylori* infection by one or more of the following methodologies: gastric biopsy using histochemical staining, tissue culture, the 14C-urea breath test (UBT), the 13C-UBT and/or faecal antigen; (3) were requested to undergo an endoscopy before the eradication treatment if they have alarm symptoms, a family history of gastric cancer or age over 40 years old without undergoing an endoscopy before and (4) voluntarily participated in the clinical trial and have signed the informed consent.

Exclusion criteria

Potential participants will be screened on the following exclusion criteria: (1) participants had a history of using antibiotics or bismuth within 4 weeks or acid inhibitor (including H2 receptor antagonist (H2RA), proton-pump inhibitor (PPI) or potassium-competitive acid blocker (P-CAB)) within 2 weeks before inclusion; (2) had an active peptic ulcer with complications such as haemorrhage, perforation or obstruction; (3) had a history of esophagectomy or gastrectomy; (4) had an allergy to any study drug; (5) were pregnant or breast feeding; (6) had a history of alcohol abuse or drug addiction; (7) existence of mental illness or (8) without self-judgement ability.

Sample size calculation

Based on previous studies, we assume the eradication rate of each group as 85%, 90% and 95%, respectively. We calculated that at least 855 participants (285 patients per treatment group) were required for recruitment for a two-sided 0.05 value of 0.05 and power of 90%, with a rate of loss to follow-up of 20%. The sample size was calculated using PASS software, V.11.0.10 (NCSS, LLC).

Recruitment, randomisation and blinding

Eligible participants will be recruited from patients diagnosed with *H. pylori* infection following the inclusion and exclusion criteria. They will be randomly assigned to three groups (group A, group B and group C) in a 1:1:1 ratio using a computer-generated algorithm for the trial treatment (figure 1). Before the treatment, the baseline characteristics of participants will be collected, including gender, sex, body mass index, family history, drug allergy history, medical history (such as basic diseases, tumour history and so on), contact information, medication history within 3 months, the history of clarithromycin medication and clinical symptoms. The blind method was applied to participants based on a comprehensive evaluation of the feasibility of the study.

Study protocol

Eight hundred and fifty-five participants were randomly divided into three groups, with 285 patients in each group, and received anti-*H. pylori* treatment as follows:

- **Group A (amoxicillin- and clarithromycin-based BQT):** 10 mg rabeprazole and 200 mg colloidal bismuth were orally taken 0.5 hours before breakfast and dinner, and 1 g amoxicillin and 500 mg clarithromycin were orally taken 0.5 hours after breakfast and dinner. The above medicines are required to be taken within 2 hours every time and continuously for 14 days. 6–8 weeks after the treatment is finished, the kit for 13C-UBT or 14C-UBT will be reviewed.

- **Group B (clarithromycin medication history-based BQT):** Participants with clarithromycin medication history: 10 mg rabeprazole and 200 mg colloidal bismuth were orally taken 0.5 hours before breakfast and dinner, and 1 g amoxicillin and 100 mg furazolidone were orally taken 0.5 hours after breakfast and dinner. The above medicines are required to be taken within 2 hours every time and continuously for 14 days. 6–8 weeks after the treatment is finished, the kit for 13C-UBT or 14C-UBT will be reviewed.

- **Group C (antimicrobial susceptibility test-based BQT):** Faecal molecular antimicrobial susceptibility tests using PCR kits detecting 23S ribosomal RNA point mutations (Jiangsu Cownik Biotechnology, Taizhou, Jiangsu, China) related to clarithromycin and levofloxacin will be performed before the treatment. DNA from stool samples will be extracted using auto nucleic acid extraction instrument CWE 9600 (Thermo Fisher Scientific, Waltham, Massachusetts). The mutations in 23S rRNA and gyrA genes will be amplified using real-time PCR using ABI 7500 (Thermo Fisher Scientific, Waltham Massachusetts). The treatment regimen will be chosen according to the results of the antimicrobial susceptibility tests. Clarithromycin-sensitive participants: 10 mg rabeprazole and 200 mg colloidal bismuth were orally taken 0.5 hours before breakfast and dinner, and 1 g amoxicillin and 500 mg clarithromycin were orally taken 0.5 hours after breakfast and dinner. Clarithromycin-resistant participants: 10 mg rabeprazole and 200 mg colloidal bismuth were orally taken 0.5 hours before breakfast and dinner, and 1 g amoxicillin and 100 mg furazolidone were orally taken 0.5 hours after breakfast and dinner. The above medicines are required to be taken within 2 hours every time and continuously for 14 days. 6–8 weeks after the treatment is finished, the kit for 13C-UBT or 14C-UBT will be reviewed.

During the trial, the investigators need to maintain close contact with the participants to dynamically master participants’ compliance and provide guidance to them.
Study endpoints

Primary outcomes
The primary end point of this trial is eradication rates in each group. The kit for the $^{13}$C-UBT or $^{14}$C-UBT will be reviewed 6–8 weeks after the eradication treatment, and a negative result (<4.0%, delta over baseline of $^{13}$C-UBT; <100, disintegrations per minute of $^{14}$C-UBT) indicated a successful eradication. Patients were not permitted to take PPIs or P-CABs 2 weeks before the UBT or antibiotics 4 weeks before the UBT. Eradication rate=number of negative cases/total cases×100%.

Secondary outcomes
The secondary end points were the incidence of AEs and compliance.

We will measure AEs and compliance with a questionnaire following the completion of treatment. Good compliance will be defined as taking at least 80% of the pills. Participants’ symptoms during the treatment such as nausea, vomiting, diarrhoea, rash, hiccups, abdominal pain, abdominal distension or other increased symptoms will be recorded. They will be divided into three categories according to the impact on daily life: mild (transient, well tolerated), moderate (some discomfort that interfered with daily life) and severe (significant discomfort that adversely affected daily life).

Safety assessments
The investigator will maintain close contact with the participants during the trial, record all AEs mentioned above on the case report form and offer medical support if necessary.

Data management
A specific data collection group will be established at the Department of Gastroenterology of SAHZU before the study. Two specific investigators with rich experience in data collation and analysis are responsible for the data collection and double check. The original data will be recorded on case report forms and an Excel (V.2022) chart accordingly and cross checked by the head investigator. All management processes associated with data
access and analysis will be supervised by the Ethics Committees of SAHZU.

Statistical analysis
Non-normally distributed continuous variables will be presented as median and categorical variables as absolute frequencies (proportions). Continuous variables will be compared using the non-parametric Kruskal-Wallis test. Categorical variables will be compared using the $\chi^2$ test. Statistical significance was defined as p<0.05. Statistical analyses will be performed using SPSS (V.26.0; IBM SPSS Statistics, IBM Corporation, Armon, New York) and GraphPad PRISM software (V.9.0; GraphPad Software, San Diego, California).

Patient and public involvement
No patients or members of the public participated in the conception of our study. The adverse reactions of patients during the trial need timely feedback for safety considerations. On completion, the final results will be fed back to the patients in case report forms and the results of the study will be published in the appropriate journal.

Ethics and dissemination
This study was approved by the Ethics Committee of SAHZU (No. 20230103). Any amendment to the research protocol will be submitted for ethical approval. All participants or his/her authorised agent must provide written informed consent (online supplemental material 1) before participating in the practice. On completion, the results of the study will be published in the appropriate peer-reviewed journal.

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Contributors
JY, QD and YWu conceptualised the study. JY, QD, HW and YWu are responsible for managing the processes of the trial. Wuang, XL, DL, GL, YL and HW supervised the field study. YWu and JY developed the first draft of the manuscript. YWu, JY and HW developed the revision of the manuscript. All the authors contributed to the development of the study protocol and approved the final draft of the manuscript.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES


知情同意书  Informed Consent

尊敬的先生/女士:

Dear Sir/ Madam

我们邀请您参加一项“基于粪便分子药敏试验的四联疗法作为一线治疗幽门螺杆菌感染的疗效研究”的临床研究，在您决定是否参加这项研究之前，请仔细阅读以下内容，帮助您了解该项研究。如果您愿意，您可以向医生询问，以确定您理解有关内容。

You will be invited to participate in a randomized controlled clinical study named “Efficacy of quadruple therapy based on fecal molecular antimicrobial susceptibility tests as a first-line treatment for Helicobacter pylori infection”. Please read the informed consent to help you understand the study before you decide whether to participate in the study or not. If you have any questions, please consult the doctor to make sure you understand the study.

1. 研究目的
   1. Objectives

   (1) 阐明基于粪便分子药敏试验的铋剂四联疗法作为一线治疗幽门螺杆菌感染的疗效。
   (2) 基于粪便分子药敏试验的铋剂四联疗法作为一线治疗幽门螺杆菌感染的安全性及经济效益分析。

   (1) To elucidate the efficacy of bismuth quadruple therapy based on fecal molecular antimicrobial susceptibility tests as the first-line treatment for Helicobacter pylori infection.
   (2) Safety and economic-benefit ratio analysis of bismuth quadruple therapy as first-line treatment for Helicobacter pylori infection based on fecal molecular antimicrobial susceptibility tests.

2. 研究背景
   2. Background

幽门螺杆菌（*Helicobacter pylori, H. pylori*）在 1994 年被世界卫生组织列为 I 类致癌原，与多种消化道疾病如慢性胃炎、消化性溃疡、胃癌以及胃 MALT 淋巴瘤密切相关。我国是 H. pylori 高感染率国家，H. pylori 感染未经治疗几乎难以自愈。H. pylori 对抗生素的耐药率逐年升高，成为根除率不断降低的主要原因之一。首次根除失败容易导致细菌耐药的产生，增加再次治疗的难度，因此尽可能在首次根除治疗时及成功根除 H. pylori。近年来，粪便分
子药敏的发展使 H. pylori 药敏试验避免了有创操作的取材方式，从胃黏膜组织活检跨越到粪便标本的全新时代。更为方便的取材方式使得基于药敏结果的初次治疗有大范围普及的可能。本研究旨在探究基于粪便分子药敏试验的四联疗法作为一线治疗幽门螺杆菌感染的疗效，为粪便分子药敏试验在中国幽门螺杆菌感染初次治疗中的价值提供更多证据。

Helicobacter pylori (H. pylori) was listed as the Class I carcinogen by the World Health Organization in 1994, and is closely associated with a variety of digestive tract diseases, such as chronic gastritis, peptic ulcer, gastric cancer and MALT lymphoma. The infection rate of H. pylori in our country is very high and the infection can hardly be healed without treatment. The resistance rate of H. pylori to antibiotics increased year by year, which became one of the main reasons for the decreasing eradication rate. Failure of initial eradication is likely to lead to bacterial resistance and increase the difficulty of re-treatment, so it is better to eradicate H. pylori at the first time successfully. In recent years, the development of molecular drug sensitivity in feces has made H. pylori antimicrobial susceptibility tests avoid invasive sampling methods. More convenient sampling methods make it possible to popularize the initial treatment based on antimicrobial susceptibility tests results. This study is aimed to explore the efficacy of quadruple therapy based on fecal molecular antimicrobial susceptibility tests as the first-line treatment of H. pylori infection, and to provide more evidence for the value of fecal molecular antimicrobial susceptibility tests in the first-line treatment of H. pylori infection in China.

3. 研究内容和步骤

3. Procedures

符合幽门螺杆菌根除研究的患者将随机进入不同的治疗组。幽门螺杆菌治疗疗程14天，治疗结束后6-8周，采用13C-尿素呼气试验或14C-尿素呼气试验评估 Hp 根除情况。研究起止时间：伦理通过、完成临床注册之日起，项目为期1年。

Patients eligible for the H. pylori eradication study will be randomized to a different treatment group. H. pylori was treated for 14 days and was assessed by 13C-urea breath test or 14C-urea breath test 6-8 weeks after completion of treatment. Study duration: 1 year from the date of ethical approval and completion of clinical registration.

如果您同意参与这项研究，我们将会安排您进入治疗组。受试者总量为855例，随机分为3组，进入各组的概率为33%，各组详细治疗方案如下述。
If you agree to participate in the study, we will place you in the treatment group. A total of 855 subjects were randomly divided into 3 groups with a 33% probability of entering each group. The detailed treatment plan for each group is as follows.

Prior to treatment, we will collect your clinical information, including sex, sex, body mass index (BMI), family history, drug allergy, medical history (such as underlying disease, tumor history, etc.), contact information, medication history within 3 months, clarithromycin medication history, clinical symptoms, etc. You will then be randomized to one of the three treatment groups to receive the appropriate medication, which will be discontinued after 14 days of prescribed medication. You will be scheduled for a review of the $^{13}$C-UBT or $^{14}$C-UBT 6-8 weeks after discontinuation.

Researchers will stay in close contact with you during the trial and provide you with medical support if necessary to help you complete your treatment more efficiently and safely. Your data will only be used for scientific research.

1) 治疗分组

1) Groups

*Group A: clarithromycin-based BQT (N=285)

- Rabeprazole 10 mg BID
- Colloidal bismuth 200 mg BID
- Amoxicillin 1 g BID
- Clarithromycin 500 mg BID for 14 Days

*Group A组：以阿莫西林和克拉霉素为基础的铋剂四联疗法：285例

- 雷贝拉唑 10 mg BID
- 果胶铋 200 mg BID
- 阿莫西林 1 g BID
- 克拉霉素 500 mg BID 疗程 14 天
* Group B: clarithromycin medication history-based BQT (N=285)

with clarithromycin medication history:
- Rabeprazole 10 mg BID
- Colloidal bismuth 200 mg BID
- Amoxicillin 1 g BID
- Furazolidone 100 mg for 14 Days

with no clarithromycin medication history:
- Rabeprazole 10 mg BID
- Colloidal bismuth 200 mg BID
- Amoxicillin 1 g BID
- Clarithromycin 500 mg BID for 14 Days

* C组：基于粪便分子药敏试验的铋剂四联疗法：285例

先进行粪便分子药敏试验，根据克拉霉素耐药结果选择下述方案。

克拉霉素敏感：
- 雷贝拉唑 10 mg BID
- 果胶铋 200 mg BID
- 阿莫西林 1 g BID
- 克拉霉素 500 mg BID 疗程 14 天

克拉霉素耐药：
雷贝拉唑 10 mg BID
果胶铋 200 mg BID
阿莫西林 1 g BID
呋喃唑酮 100 mg BID
疗程 14 天

*Group C: antimicrobial susceptibility tests-based BQT (N=285)
clarithromycin-sensitive:
rabeprazole 10 mg BID
colloidal bismuth 200 mg BID
amoxicillin 1 g BID
clarithromycin 500 mg BID for 14 Days
clarithromycin-resistant:
rabeprazole 10 mg BID
colloidal bismuth 200 mg BID
amoxicillin 1 g BID
furazolidone 100 mg for 14 Days

2) Study flow charts
4. Risk

This study may result in adverse reactions related to the treatment drugs, mainly including nausea, vomiting, abdominal distension, abdominal pain, fever, rash, etc. If you have any questions related to this study, please contact your attending physician or the office at 0571-89713734 during office hours. If you have any questions related to your rights/interests, or if you would like to report any difficulties, grievances or concerns encountered in this study, or if you would like to provide comments and suggestions related to this study, please contact the Ethics Committee of the Hospital or the Ethics Review Committee of the Second Affiliated Hospital of Zhejiang University Medical School. The hospital will seek reimbursement from the insurance company for you in the event of...
serious adverse events related to this study that exceed expectations and result in serious consequences and meet the terms of clinical research liability insurance insured by the hospital.

5. 研究可能的获益

5. Benefits

参加本项研究，您有可能获得部分检查费用（粪便分子药敏试验）的减免及直接的医疗受益，比如幽门螺杆菌的治疗成功、慢性胃病好转、身心健康的恢复等，并且会有专业的研究人员全程指导您完成治疗疗程及复查事宜。我们希望从您参与的本研究中得到的信息在未来能够使与您的病情相同的病人获益。研究对您可能没有上述的直接医疗受益。

Participating in this study, you may be able to get part of the cost of examination (fecal molecular antimicrobial susceptibility tests) reduced and direct medical benefits, such as the successful treatment of \emph{H. pylori}, the improvement of chronic stomach disease, physical and mental health recovery, and professional researchers will guide you through the treatment course and review. We hope that the information gained from your participation in this study will benefit patients with the same condition as you in the future. The study may not have the above direct medical benefits for you.

本研究中得到的信息将可能有助于了解基于粪便分子药敏试验的四联疗法作为一线治疗幽门螺杆菌感染的疗效，为粪便分子药敏试验在中国幽门螺杆菌感染初次治疗中的价值提供更多证据，造福更多的幽门螺杆菌感染患者。

The information obtained in this study may help to understand the efficacy of quadruple therapy based on fecal molecular antimicrobial susceptibility tests as the first-line treatment of \emph{H. pylori} infection, and provide more evidence for the value of fecal molecular antimicrobial susceptibility tests in the initial treatment of \emph{H. pylori} infection in China, benefiting more patients with \emph{H. pylori} infection.

6. 研究相关费用及补偿

6. Expense and Compensation

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<td>Rabeprazole</td>
<td>波利特</td>
<td>10</td>
<td>12.86</td>
<td>Eisai China Inc.</td>
</tr>
<tr>
<td>Colloidal bismuth</td>
<td>果胶铋</td>
<td>100</td>
<td>0.48</td>
<td>Shanxi Ante Bio-pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>诺莫灵</td>
<td>250</td>
<td>0.07</td>
<td>Cspc Hebei Zhongrun Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>痢特灵</td>
<td>100</td>
<td>0.17</td>
<td>Tianjin Lisheng Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>克拉仙</td>
<td>250</td>
<td>7.33</td>
<td>Shanghai Abbott Pharmaceutical Co., Ltd.</td>
</tr>
</tbody>
</table>

The drugs mentioned above are routinely used in the outpatient Department of Gastroenterology of the Second Affiliated Hospital of Zhejiang University Medical College, and the fees were settled according to the unified price of the hospital pharmacy during the trial (the unit price of drugs per table is just for reference, and final price shall be according to the actual price during the trial).

The treatment cost of each treatment plan is described as follows: The treatment cost of rabeprazole + bismuth pectin + amoxicillin + clarithromycín will be about 805.28 yuan; The treatment cost of rabeprazole + bismuth pectin + amoxicillin + furazolidone will be about 399.56 yuan. Treatment costs will not be waived in all three groups. The cost of fecal antimicrobial susceptibility tests in this study will be borne by the project team, and the cost of post-treatment

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review will be borne by yourself.

在研究期间，如果您发生与本研究药物相关的不良事件或严重不良事件时，医生会采取积极的措施及时进行处理。如发生健康损害时，依据国家法律法规，研究者将对您进行相应的补偿。

If you have adverse events or serious adverse events related to the drugs during the study period, the doctor will take measures in time. In the event of health damage, according to national laws and regulations, researchers will compensate you accordingly.

7. 遵从的义务
7. Obligation

在整个研究期间，您必须遵守本品研究方案的有关规定，配合医护人员，详细记录试验相关的信息资料，保证研究资料的真实性。如果您未经负责医生的同意使用其他药物，或有妨碍研究完成的行为，研究人员可要求您退出试验，或提前终止试验。

During the whole research period, you must abide by the relevant regulations of the research protocol, cooperate with the medical staff, record the relevant information of the study in detail, and ensure the authenticity of the data. If you use other drugs without the consent of the doctor, or if there is an act that hinders the completion of the study, the researcher may ask you to withdraw from the study or terminate the study in advance.

8. 可能获得的其他备选治疗方案及其受益和风险
8. Alternative therapeutic regimens, risks and benefits

目前临床多采用联合用药来清除幽门螺杆菌感染，本研究中含铋剂四联疗法为首选的一线治疗方案。此外，其他备选的治疗方案包括：包含四环素的治疗方案等其他含铋剂四联疗法。若您不愿意参加本研究，您也可以选择自行咨询医生，针对您的个体情况选择治疗方案。不同治疗方案对清除幽门螺杆菌感染均可能有效或无效的。

Combination drugs, usually, are adopted to eradicate *H. pylori* infection at present. The bismuth-containing quadruple therapy is the first-line treatment. In addition, alternative treatment options include quadruple therapy with quinolone, etc. If you are not willing to participate in this study, you can also consult the doctor and choose regimen. Different treatments may effective or ineffective in eradicating *H. pylori* infection.
9. Voluntary

Participation in this study is voluntary and you could refuse to participate or withdraw at any time and there will not be any punishment or unfair treatment. You should inform the doctor if you plan to withdraw the study. If this study is detrimental to you for continuing to participate in, the physician has the right to terminate your participation in this study at any time. The ethics committee and the investigators may also stop this study. The doctor will ask you to do the exit examinations before you withdraw from the study. Data obtained prior to withdrawal may still be used under the relevant laws/regulations.

10. Privacy issue

Your personal data in and during the study are confidential, but researchers, inspectors, members of the ethics committee or drug administration may refer to your personal data in the research unit as required. No information about you will be disclosed if the results of this study are published. Signing this document indicates that you have authorized the researchers to use your medical data.

You agree that the data obtained in this study, including all examination results, will be kept in the
researcher's computer and paper documents, and your name will be covered in data. These data may be used for registration in China or other countries. In the process, the sponsors will use these data and save them in accordance with the relevant laws and regulations.

我们将储存本项目所采取的粪便等样本，并可能在以后的研究中使用，所有样本上贴有带编码的标签，不会出现您的姓名，您的所有信息将会保密。

The stool samples collected in this study will be stored and may be used in future studies. All specimens are labeled with codes not appear your name. All your information will be kept confidential.

11. 伦理委员会
11. Ethics committee

本研究已向浙江大学医学院附属第二医院人体研究伦理委员会报告，经委员会的全面审查和包括对受试者的风险评估，并获得了批准。在研究过程中，有关伦理和权益事宜可联系浙江大学医学院附属第二医院人体研究伦理委员会，电话：白天 0571-87783759；晚上（总值班）：13757118366；邮箱地址：HREC2013@126.com

This study was reported to the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine, and was approved after a comprehensive review by the committee, including a risk assessment for subjects. During the course of the study, for ethical and rights issues, please contact the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine, tel: Day 0571-87783759; Evening (general duty) 13757118366; Email address: HREC2013@126.com

我确认已阅读并理解了本研究的知情同意书，自愿接受本研究中的治疗方法，并同意将我的医疗数据用于本研究的发表。

I confirm that I have read and understood the informed consent form for this study. I voluntarily accept the treatment in this study, and consent to the use of my medical data for publication of this study.

受试者签名: ___________ 联系电话: ___________ 日期: ___________

Participator’s name: ___________ Telephone: ___________ Date: ___________

代理人签名: ___________ 与受试者关系: ___________ 联系电话: ___________
Agent's name:  
Kinship:  
Telephone:  

Date:  
(If possible) 
Witness (if possible):  
Telephone:  
Date:  

我确认已向患者解释了本研究的详细情况，包括其权利以及可能的受益和风险，并且保证随时解答患者关于本项临床研究信息的咨询。

I confirm that I have explained to the patient the details of the study, including rights, possible benefits and risks, and assure to answer the patient's consult on this clinical study at any time.

Investigator's name:  
Telephone:  
Date:  

Wu Y. et al. BMJ Open 2023; 13:e072670. doi: 10.1136/bmjopen-2023-072670