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# Application of a semi-automatic, intensive follow-up for improving efficacy and adherence of *Helicobacter pylori* eradication therapy: A randomized controlled trial

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## Abstract

A complete understanding and good adherence are crucial for successful *Helicobacter pylori* eradication. Proper frequency of reminders might be helpful to both doctors and patients to maintain adherence during treatment. The study was to evaluate the influence of an intensive follow-up system based on a clinical database on *H. pylori* eradication therapy. A total of 196 eligible patients were equally and randomly divided into an intensive follow-up group and a control group. Both groups were administered bismuth-containing quadruple therapy for 14 days. Patients in the intensive follow-up group were informed of pre-treatment, including the duration and potential adverse events. Subsequently, they received telephone follow-ups on days 3 and 14 and 3 days before the urea breath test (UBT). The time points were automatically reminded by a follow-up system in the established clinical database. The control group was only informed of pre-treatment information. UBT was performed 4 weeks after treatment in both groups to assess the *presence of H. pylori*. The eradication rate, patient compliance, and adverse events were calculated and compared. The *H. pylori* eradication rates of the intensive follow-up and control groups were 94.7% (90/95, 95% CI: 90%–99%) and 92.9% (78/84, 95% CI: 87%–98%), respectively, by PP analysis ($p$ = 0.601), and 91.8% (90/98, 95% CI: 86%–97%) and 81.6% (80/98, 95% CI: 74%–89%) by ITT analysis ($p$ = 0.035). Adverse events occurred in 9 intensive follow-up group patients and 12 in the control group. Adherence was 96.9% (95/98) in the intensive follow-up group and 85.7% (84/98) in the control group. Semi-automatic intensive follow-up contributed to a higher eradication rate and adherence to *H. pylori* treatment.

**KEYWORDS**
adherence, bismuth-containing quadruple therapy, follow-up, *Helicobacter pylori*

Yao Chen and Hongxun Yuan are co-first authors.

## 1 | INTRODUCTION

*Helicobacter pylori* (*H. pylori*), classified as a Group 1 carcinogen by the World Health Organization, is known to cause 75% of the cases of gastric cancer worldwide (De Martel et al., 2012). China is a country with a high rate of *H. pylori* infections and a high prevalence rate of gastric cancer (Chen et al., 2016; Cheng et al., 2009). The eradication of *H. pylori* can reduce the incidence of gastric cancer (Pan et al., 2016). However, *H. pylori* eradication therapy has been compromised due to multiple reasons, especially antibiotic resistance and poor patient compliance (Fagoonee & Pellicano, 2019; Flores-Treviño et al., 2018; Savoldi et al., 2018).

Adherence to therapy is the single most important factor in *H. pylori* eradication. It is influenced by several factors, including the complexity and duration of treatment, side effects, patient willingness, patient education and socioeconomic background, and physician motivation (Burkhart & Sabaté, 2003; Li et al., 2018; O'Connor et al., 2009). The recommended eradication therapy in China had been upgraded to quadruple therapy with a duration of 14 days since 2013 (Liu et al., 2013). The complexity and longer duration brought challenges for both physicians and patients. A retrospective study revealed that approximately 17% of patients showed poor compliance in their treatment history, primarily due to the patients' own will and side effects (Li et al., 2018). The majority of the studies concluded that enhancing follow-up using a telephone, short message, diary chart, and social media platforms could positively improve the eradication rate (Al-Eidan et al., 2002; Luo et al., 2020; Wang et al., 2019) or reduce side effects (Wang et al., 2015). Particularly, intensive follow-up requires a greater effort from the physician. It was challenging to burden Chinese doctors with additional intensive follow-up work in real life. Moreover, overly frequent patient education might not be necessary, and perhaps, it was offensive to the patient. It might be a better and more acceptable approach to remind the patient at certain key time points during the treatment. Therefore, a follow-up tool that requires little energy from the physician is required.

To manage the *H. pylori* patients semi-automatically, we developed a clinical database system that helped doctors record patient information and send follow-up information at planned time points. Therefore, we conducted a randomized controlled trial and analyzed the correlations among the patient adherence, the *H. pylori* eradication rate, and adverse events (AEs) to evaluate the effect of the enhanced follow-up on *H. pylori* eradication, which also helps to popularize the database system further.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and participants

This study was an open, prospective trial conducted on *H. pylori* outpatients in the Department of Traditional Chinese Medicine of Peking University International Hospital and the Department of Integrative TCM and Western Medicine of Peking University First Hospital from March to December 2019. This study was a pilot study to explore the influence of an intensive follow-up system based on a clinical database on *H. pylori* eradication therapy. The database used in this study is the "*Helicobacter pylori* diagnosis and treatment database," which was commissioned by the research team in 2016 and developed by Beijing Relinsal Technology Co. It is a proprietary system and a specialist database for *H. pylori* infection.

The inclusion criteria were as follows: (a) *H. pylori* infection confirmed by $^{13}C/^{14}C$-urea breath test (UBT), rapid urease test, or stool antigen test within 15 days; (b) no history of *H. pylori* eradication treatment; (c) age ranging between 18 and 70 years, no limitations to gender; and (d) volunteer adults (or legal representatives) agree to give written informed consent.

The exclusion criteria included the following: (a) known allergy to drugs used in this study; (b) history of surgery or active bleeding in the upper gastrointestinal tract; (c) the administration of antibiotics, bismuth, acid inhibitors, or antibacterial Chinese medicine within 1 month; (d) suffering from severe diseases affecting the evaluation of the study (e.g., cognitive disorder, severe liver, heart and kidney diseases, cancer, and alcoholism; (e) pregnant or lactating women; (f) patients with difficulty in expressing subjective feelings; and (g) inaccessibility by telephone.

### 2.2 | Intervention

The eligible patients were randomly and equally divided into an intensive follow-up group and a control group. All patients were prescribed bismuth-containing quadruple therapy for 14 days as follows: esomeprazole (AstraZeneca, SFDA approval number H20046379) 20 mg, amoxicillin (Zhuhai United Laboratories, SFDA approval number H20003263) 1000 mg, clarithromycin (Abbott Inc., SFDA approval number H20033044) 500 mg, and bismuth potassium citrate (Livzon Inc., SFDA approval number H10920098) 220 mg. All the drugs were administered twice daily. The treatment lasted for 14 days, and the drugs were recycled after treatment.

For the intensive follow-up group, the details of the drug administration and possible adverse effects were informed in detail before therapy, including the dosage, frequency, course of medications, and the potential adverse effects, such as bitter taste and melena. Meanwhile, we set the reminder on days 3, 14, and 40 (3 days before the UBT) counted from the first day of treatment in the database's follow-up system. The database automatically outputted the list of follow-up time points and content for each patient and reminded the researchers to conduct the follow-up procedure in time. The main contents of follow-up included the following: (a) the reminder about drug dosage and time, (b) AEs, (c) precautions for home care, and (d) reminder about the time for drug withdrawal and revisit.

For the control group, we pointed out the notes of treatment and time to revisit without follow-up during treatment. Both the intensive follow-up and the control groups underwent the final revisit, including $^{13}C$-UBT, 4 weeks after the drug treatment.

The basic information of the participants, clinical data, treatment protocol, adherence, and AEs was collected and recorded in

the corresponding standardized module of *the H. pylori* diagnosis and treatment database.

### 2.3 | Primary outcome

*H. pylori* eradication rate: The participants underwent a $^{13}$C-UBT 4 weeks after the treatment. Therapy was considered successful upon obtaining negative UBT results. If the delta-over-baseline (DOB) value is between 2 and 6, the UBT should be re-evaluated after 2 weeks to avoid false-negative or false-positive results.

### 2.4 | Adherence

The medication adherence was evaluated by determining the number of recycled drugs. A dose/expected dose <90% was considered to indicate poor adherence. The patients exhibiting poor adherence were excluded from the per-protocol (PP) analysis.

### 2.5 | Adverse events

Any abnormal reactions were recorded in both groups.

### 2.6 | Statistical analysis

Data were entered and analyzed using SPSS 24.0. The *H. pylori* eradication rate was evaluated as described above. The intention-to-treat (ITT) and per-protocol (PP) analyses were performed for comparison using the chi-square test or precise probability test. AEs are presented as the number and percentage of patients. The details of AEs were recorded in the lists. Bilateral tests were applied to all statistical analyses, and $p < 0.05$ was considered statistically significant.

## 3 | RESULTS

### 3.1 | Characteristics of patients

This study included 196 patients, who provided consent. The intensive follow-up group was composed of 50 male patients and 48 female patients, with an average age of 43.12 ± 12.79 years. The control group included 55 male patients and 43 female patients with an average age of 43.95 ± 12.07 years. The comparison of basic information between the two groups showed no statistical significance, such as gender, age, height, and body weight.

### 3.2 | Eradication rate

In the intensive follow-up group, three patients were excluded from the PP population (two AEs and failed treatments, one lost contact). *H. pylori* was eradicated in 90 of the remaining 95 patients. The eradication rates were 94.7% (90/95, 95% CI: 90%–99%) by PP analysis and 91.8% (90/98, 95% CI: 86%–97%) by ITT analysis.

In the control group, 14 patients were excluded from the PP population (5 AEs with treatment failure, 9 patients with poor adherence, 2 patients with successful eradication, and 7 patients with treatment failure). Of the remaining 84 patients who completed the treatment and follow-up, 78 patients succeeded, and 6 failed. Thus, the eradication rates were 92.9% (78/84, 95% CI: 87%–98%) by PP analysis and 81.6% (80/98, 95% CI: 74%–89%) by ITT analysis, respectively. There was no statistically significant difference in the PP analysis results between the two groups ($x^2 = 0.273$, $p = 0.601$). The ITT analysis between the two groups showed a significant difference in the eradication rate ($x^2 = 4.434$, $p = 0.035$). The details are shown in Table 1 and Figure 1.

**TABLE 1** The eradication rate of *H. pylori*

| | Intensive follow-up group (*n*) | Control group (*n*) | *p*-value |
|---|---|---|---|
| Total patients | 98 | 98 | |
| Cured patients | 90 | 80 | |
| Uncured patients | 5 | 13 | |
| ITT | 90/98 (91.8%) | 80/98 (81.6%) | 0.035 |
| PP | 90/95 (94.7%) | 78/84 (92.9%) | 0.601 |
| Good adherence | 95 (96.9%) | 84 (85.7%) | 0.005 |

### 3.3 | Adherence

In the intensive follow-up group, 2 patients stopped treatment after 3–5 days due to skin rash, and 1 patient lost contact. The adherence rate was 96.9% (95/98). In the control group, 14 patients showed poor adherence, of whom 5 patients took <50% of the drugs because of the bitter taste, melena, and rash, and 9 cases were due to other reasons (Table 2). The remaining 84 patients showed good adherence, resulting in an adherence rate of 85.7% (84/98). The comparison of adherence in the two groups was evaluated using the Pearson's chi-square test with $p = 0.005$. The small number of patients with poor adherence in the intensive follow-up group precluded us from conducting a subgroup analysis because of poor adherence. This may reflect the small sample size involved rather than the actual lack of difference.

### 3.4 | Adverse events

In total, 21 patients experienced AEs in both groups. The main symptoms included rash, nausea, diarrhea, poor appetite, abdominal distention, and edema, among which 9 patients were in the intensive follow-up group (9/98) and 12 patients in the control group (12/98). The AE rate was not significantly different between the two groups ($x^2 = 0.48$, $p = 0.488$), as shown in Table 3.

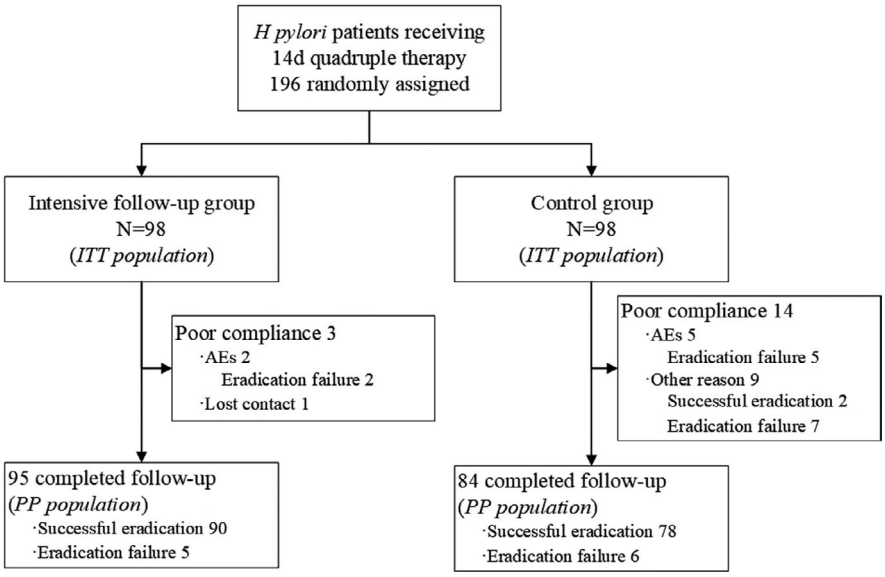


**FIGURE 1** Trial profile. AEs, adverse events; ITT, intention-to-treat; and PP, per-protocol

**TABLE 2** Low adherence reasons

| Reasons | Patients (*n*) | Specific information |
|---|---|---|
| Excessive panic | 4 | Withdrawal of drug because of bitter taste and melena |
| Adverse reactions | 1 | Withdrawal of drug due to rashes |
| Forgetting | 7 | Loss of drugs or forgetting drug administration |
| Exhaustion to drugs | 1 | Drug dosage reduction based on own idea considering the big adverse effect |
| Others | 1 | Against clinician's directions and taking medicine based on medicine instructions |
| Total | 14 | |

**TABLE 3** AEs

| AEs | Intensive follow-up group (*n*) | Control group (*n*) | *p*-value |
|---|---|---|---|
| Rash | 2 | 1 | |
| Nausea | 4 | 5 | |
| Diarrhea | 4 | 5 | |
| Edema | 0 | 1 | |
| Abdominal distention | 2 | 3 | |
| Poor appetite | 3 | 5 | |
| In total | 9 | 12 | 0.488 |

## 4 | DISCUSSION

The failure of *H. pylori* eradication therapy might be due to several factors, including the bacterial strain, the patient's physical and psychological health, and environment (Saracino et al., 2020; Wermeille et al., 2002; Yokota et al., 2019). The most prevalent reason for this is the antibiotic resistance of *H. pylori*. The treatment plan was developed from a triple-drug combination to quadruple-drug therapies in recent years (Malfertheiner et al., 2017; Matsumoto et al., 2019). Additionally, the therapy duration was gradually increased to 14 days. It is possible for certain drugs, such as metronidazole, to overcome drug resistance by an increase in the dosage (Ji & Lu, 2018). However, any ideal solution relies on the strict implementation of drug administration to eradicate *H. pylori* infection.

At present, the recommended bismuth-containing quadruple therapy is associated with poor patient adherence with reasons for multiple types of drugs, long treatment course, and a higher risk of adverse reactions (Malfertheiner et al., 2017). Based on previous research, the failure rate of *H. pylori* eradication in patients withdrawing drugs was 4.26 times that of those who maintained therapy (Li et al., 2015). Poor adherence has been another important factor impeding eradication therapy (Kotilea et al., 2017; Shakya Shrestha et al., 2016). The leading causes of poor adherence include forgetting to take drugs and failure to relieve the clinical symptoms during treatment (Kotilea et al., 2017; Shakya Shrestha et al., 2016). Therefore, increasing patient adherence and paying more attention to patients' health education during eradication therapy is crucial.

To tackle this problem, several compliance reinforcement measures, such as a medication chart/calendar, mini pillbox, and telephone/short-message-based re-education, have been evaluated in previous studies. A study using a short message as a reminder could improve the eradication rate and compliance (Wang et al., 2019); however, it spent more energy and time sending messages to each patient twice daily. In contrast, telephone-based daily reminders had no significant impact on patient compliance or *H. pylori* eradication (Wang et al., 2015). A recent study using a popular social media platform as a patient reminder at four time points during treatment acquired better eradication efficacy and compliance (Luo et al., 2020). However, it did not undergo ITT and PP analysis, and doctors still needed to record every patient's information by themselves. Intensive follow-up requires more attention and energy from investigators, and manual recording is tedious and easy to omit. Such intensive visits not only exhausted the physician's energy, but may also make some patients feel uncomfortable or offended. Moreover, the physicians in China were exhausted from dealing with an overload of patients daily and hardly had spare energy for intensive follow-ups (Fu et al., 2018).

Based on a previously established clinical database, we designed a semi-automatic follow-up system to overcome this problem. We added a follow-up function to the clinical database of *H. pylori* to remind the investigators the day before the follow-up visit with the patient list, ensuring accurate implementation of the intensive follow-up. The advantage of the database is that it automatically generated a follow-up and reminder plan with uploaded patient information, which maintained the accuracy and efficiency of busy clinicians. Here, we introduced the concept of enhanced priority time follow-up, which meant that active contact was made by the investigator on days 3, 7, and 14 from the first day of treatment and 3 days before the UBT test. Contact at day 3 aimed to ensure that the patient fully understood the medication regimen, that is, the right dosage and frequency. Contact at day 7 focused on the occurrence of AEs, and contact at day 14 was to remind the patients to stop the treatment.

As we observed, patients undergoing the initial treatment had a higher possibility of taking the wrong doses of medication or forget to take the drugs. However, patients who received remedial therapy had higher expectations for successful treatment and a clearer understanding of the whole therapy with better adherence. In practice, there were many patients in the initial treatment, the failure of whose treatment would lead to increased antibiotic resistance of *H. pylori*, causing a waste of medical resources and aggravating stress to patients and their families (Liu et al., 2019). Therefore, additional attention should be paid to the drug adherence of patients during the initial treatment. A reasonably intensive follow-up and timely reminder should be given.

Our study showed that the adherence in the intensive follow-up group was 96.9% (95/98) and higher than that in the control group (85.7%, 84/98). The ITT analysis of *H. pylori* eradication was 91.8% (90/98) and 81.6% (80/98) in the intensive and control groups, respectively. Additionally, the PP analysis was 94.7% (90/95) and 92.9% (78/84), respectively. The ITT analysis showed a statistical significance between the groups. During the follow-up in our study, we found that improper medication taking was commonly due to busy work, neglect, the loss of drugs, or the occurrence of minor AEs, such as stool color change and epigastric discomfort. These patients stopped treatment on their own, which affected the eradication rate. For this reason, researchers were asked to answer patients' questions and evaluate the response to treatment during follow-up visits, and to encourage patients experiencing a bitter taste, nausea, and mild upper abdominal discomfort to adhere to the treatment. These measures increased the patient adherence and eradication rate, which indicated that properly intensive follow-ups and better communication between the doctor and patient enabled the relief of patients' stress caused by mild AEs and increased medication adherence, thus eventually raising *the H. pylori* eradication rate.

Nevertheless, our study had several limitations. First, although our database has been established for 4 years, it is still not fully automated. We hope that at a later stage, this database will be interfaced with the hospital's HIS diagnosis and treatment system, so that we can automatically send information to our follow-up patients regularly and directly through the hospital's system. If this idea can be realized, in our future work, automatic processing of the follow-up process is expected, such as reducing the manual protocols by automatically sending standard follow-up terms, patient education texts, and questionnaires of AEs to the patients. We will be able to optimize the time and efficiency using computers. Second, the database only helped to record the patient information without providing a risk evaluation for adherence based on the patient's history. We are planning to design an adherence risk assessment tool and set up an adherence evaluation model or a checklist based on common reasons for poor adherence, making the follow-up more accurate. This measure could not only reduce the workload of investigators, but also make the follow-up more precise and efficient, and in the meantime, reduce unnecessary disturbance to patients. Third, the contents of the follow-up could be optimized and standardized according to the recommendation of trust-based patient education (Graham et al., 2016). In addition, susceptibility data were not available in this study. It might be difficult to completely understand the relationship between failure and compliance. However, in the control group, 12/14 patients with poor compliance failed the treatment, which contributed most to the failure cases. For patients undergoing *H. pylori* eradication for the first time, empirical treatment remains the mainstay of the treatment. Our previous studies showed that, with good compliance, a 14-day amoxicillin–clarithromycin-containing bismuth quadruple therapy achieved a > 90% eradication rate as the first-line therapy, despite the background of high resistance to clarithromycin in Beijing, China (Chen et al., 2020).

In summary, semi-automatic intensive follow-up can increase the therapeutic efficiency. Looking forward, if the database can be fully connected with the hospital's outpatient system and automatically send follow-up information to patients in need, patient adherence and treatment efficiency will be greatly improved. In addition, setting a patient adherence evaluation module in the database can also

enable clinicians to identify the patients with poor adherence in advance and proactively communicate with them, increasing both the efficiency of therapy and the rate of eradication.

## ETHICS STATEMENT

This study was approved by the Ethics Committee of Peking University International Hospital (grant number 2018–066 BMR).

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## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

**Yao Chen**: Data curation (Lead); Investigation (equal); Methodology (Equal); Writing-original draft (Lead); Writing-review & editing (Equal). **Hongxun Yuan:** Methodology (Equal); Software (Equal). **Hui Ye**: Conceptualization (Lead); Data curation (Equal); Investigation (Equal); Methodology (Equal); Writing-original draft (Equal); Writing-review & editing (Lead). **Zongming Shi:** Formal analysis (Equal); Investigation (Equal). **Xin Deng:** Investigation (Equal); Software (Equal). **Xuezhi Zhang:** Methodology (Equal). **Xikang Hou:** Software (Equal); Writing-review & editing (Equal).

## DATA AVAILABILITY STATEMENT

All primary data obtained in this study excluding the information related to participant identities are available in the supplementary table at Zenodo: https://doi.org/10.5281/zenodo.4382172.

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