TITLE PAGE

Title

Self-interruption of *Helicobacter pylori* eradication therapy and its associated risk factors

(Self-interruption of *H. pylori* eradication therapy)

Hiroko Ichikawa* [1, 2, 3], Yoshifumi Sugiyama* [3, 4], Rieko Mutai* [3, 5], Toshio Yamada [1], Hidetaka Wakabayashi[6], Yuko Nakano[7], Shuhei Yoshida[8], Tetsuro Hayashi[9], Shinichi Murayama[10], Masato Matsushima[3]

* These authors contributed equally to this article.

Author affiliations

1. Department of Gastroenterology and Hepatology, Tokyo Rinkai Hospital
2. Department of Gastroenterology, Eiju General Hospital
3. Division of Clinical Epidemiology, Research Center for Medical Sciences, The Jikei University School of Medicine
4. Division of Community Health and Primary Care, Center for Medical Education, The Jikei University School of Medicine
5. Department of Adult Nursing, The Jikei University School of Nursing
6. Department of Rehabilitation Medicine, Tokyo Women's Medical University Hospital

7. Veterinary Cancer Center, Hayashiya Animal Hospital
8. Department of Community-Based Medical System, Graduate School of Biomedical and Health Sciences, Hiroshima University
9. Division of Clinical Epidemiology, National Hospital Organization Tokyo Medical Center
10. Chiba-Kenaikai Aozora Clinic

Authors

Hiroko Ichikawa, MD
市川 欧子
1. Department of Gastroenterology and Hepatology, Tokyo Rinkai Hospital
東京臨海病院 消化器内科
2. Department of Gastroenterology, Eiju General Hospital
永寿総合病院 消化器内科
3. Division of Clinical Epidemiology, Research Center for Medical Sciences, The Jikei University School of Medicine
東京慈恵会医科大学 総合医科学研究センター 臨床疫学研究部
Department of Gastroenterology, Eiju General Hospital, 2-23-16, Higashiueno, Taito-ku, Tokyo 110-8645, Japan
Email: hiro51kawa@gmail.com

Yoshifumi Sugiyama, MD

杉山　佳史

4. Division of Community Health and Primary Care, Center for Medical Education, The Jikei University School of Medicine

東京慈恵会医科大学　教育センター　地域医療支援部門

Division of Community Health and Primary Care, Center for Medical Education, The Jikei University School of Medicine, 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan

Email: yoshifumi.sugiyama@jikei.ac.jp

Rieko Mutai, RN, MSN

務臺 理恵子

5. Department of Adult Nursing, The Jikei University School of Nursing

東京慈恵会医科大学　医学部看護学科　成人看護学

Department of Adult Nursing, The Jikei University School of Nursing, 8-3-1, Kokuryo-cho, Chofu-shi, Tokyo 182-8570, Japan

Email: rieko_mutai@jikei.ac.jp

Toshio Yamada, MD, PhD

山田 俊夫

1. Department of Gastroenterology and Hepatology, Tokyo Rinkai Hospital

東京臨海病院 消化器内科

Department of Gastroenterology and Hepatology, Tokyo Rinkai Hospital, 1-4-2, Rinkai-cho, Edogawa-ku, Tokyo 134-0086, Japan

Email: tosyamrinkai@gmail.com

Hidetaka Wakabayashi, MD, PhD

若林 秀隆

6. Department of Rehabilitation Medicine, Tokyo Women's Medical University Hospital

東京女子医科大学病院 リハビリテーション科

Department of Rehabilitation Medicine, Tokyo Women's Medical University Hospital, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Email: noventurenoglory@gmail.com

Yuko Nakano, DVM, PhD

中野 優子

7. Veterinary Cancer Center, Hayashiya Animal Hospital

林屋動物診療室 どうぶつ腫瘍センター

Veterinary Cancer Center, Hayashiya Animal Hospital, 18-6, Rokujizonaramachi, Uji-shi, Kyoto 611-0001, Japan
Email: yuko-n@momo.so-net.ne.jp

Shuhei Yoshida, MD, PhD
吉田 秀平
8. Department of Community-Based Medical System, Graduate School of Biomedical and Health Sciences, Hiroshima University
広島大学 大学院医歯薬保健学研究科 地域医療システム学講座
Department of Community-Based Medical System, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3, Kasumi, Minami-ku, Hiroshima-shi, Hiroshima 734-8551, Japan
Email: yoshida.shuhei.0810@gmail.com

Tetsuro Hayashi, MD, MPH, PhD
林 哲朗
9. Division of Clinical Epidemiology, National Hospital Organization Tokyo Medical Center
国立病院機構 東京医療センター 臨床疫学研究室

1 Division of Clinical Epidemiology, National Hospital Organization Tokyo Medical Center, 2-
2 5-1, Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan
3 Email: hayashi.tetsuro.nj@mail.hosp.go.jp
4
5 Shinichi Murayama, MD
6 村山 慎一
7 10. Chiba-Kenaikai Aozora Clinic
8 千葉健愛会 あおぞら診療所
9 2-357, Midorigaoka, Matsudo-shi, Chiba 271-0074, Japan
10 Email: s-mrym@nifty.com
11
12 Masato Matsushima, MD, MPH, PhD
13 松島 雅人
14 3. Division of Clinical Epidemiology, Research Center for Medical Sciences, The Jikei
15 University School of Medicine
16 東京慈恵会医科大学 総合医科学研究センター 臨床疫学研究部
17 Division of Clinical Epidemiology, Research Center for Medical Sciences, The Jikei University
18 School of Medicine, 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan
19 Email: masato@jikei.ac.jp

Correspondence

Hiroko Ichikawa, MD

Department of Gastroenterology, Eiju General Hospital, 2-23-16, Higashiueno, Taito-ku, Tokyo 110-8645, Japan

Tel: 03-3833-8381

Email: hiro51kawa@gmail.com

Acknowledgments

The authors are grateful to the members of the Division of Clinical Epidemiology, Research Center for Medical Sciences, The Jikei University School of Medicine for their valuable advice. We thank Korin Albert, PhD and Angela Morben, DVM, ELS, from Edanz Group (https://en-author-services.edanzgroup.com/ac), for editing a draft of this manuscript.

Ethical approval

This study was approved by the Ethics Committee of Tokyo Rinkai Hospital (reception number: 168) and by the Ethics Committee of The Jikei University School of Medicine (approval number: 29-295(8911)).

Key words

Helicobacter pylori, eradication therapy, self-interruption, risk factors

Abstract

Objectives To determine the incidence of self-interruption of a *Helicobacter pylori* (HP) eradication protocol and to identify its associated risk factors in Japan.

Design Retrospective cohort study with case-control study.

Setting Regional secondary care hospital located in Edogawa-ku, Tokyo, Japan.

Participants Patients met the inclusion criteria if they visited the Department of Gastroenterology and Hepatology on an outpatient basis from April 2002 to September 2014 and had a positive urea breath test (UBT) result. Patients were excluded if they took a HP test other than a UBT or were <20 years of age.

Outcome measure Self-interruption of the eradication therapy protocol, which was defined as failure to complete a scheduled post-eradication therapy UBT.

Results The descriptive analysis showed that among the 2,488 patients included in this study, 270 failed to take the post-eradication therapy UBT. Multiple logistic analyses showed that the presence of gastric and duodenal ulcers (compared with atrophic gastritis) was associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 2.220, p = 0.001). An age of ≥50 years (compared with <40 years) was less strongly associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 0.467, 0.307, and 0.185 and p = 0.011, <0.001, and <0.001, for age of 50 to <60 years, 60 to <70 years, and ≥70 years, respectively). Receiving a recommendation following a cancer screening result was also less strongly

associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 0.249, p = 0.001).

Conclusion Approximately 10% of the study participants self-interrupted the HP eradication protocol. Additionally, age <40 years and the presence of gastric and duodenal ulcers were risk factors for poor adherence.

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer deaths worldwide.[1] More than 1 million people were newly diagnosed and nearly 800,000 died of gastric cancer in 2018.[1] Although cigarette smoking, high alcohol intake, excess dietary salt, lack of refrigeration, inadequate fruit and vegetable consumption, and pernicious anemia are reported as risk factors for gastric cancer,[2] *Helicobacter pylori* (HP) is considered the most important factor.[2] In fact, HP is classified as a definitive carcinogen (Group 1),[3] and its treatment is highly recommended.[4]

Nevertheless, approximately 4.4 billion individuals are infected with HP worldwide.[5] The incidence of gastric cancer is high in East Asia, Eastern Europe, and South America, and the incidence in Japan was ranked as third highest in the world in 2018.[6] In Japan, eradication therapy for peptic ulcers caused by HP infection has been covered by public health insurance since 2000, and the coverage was expanded to chronic HP gastritis in 2013.[7]

The preventive effect of HP eradication therapy on reducing the incidence of gastric cancer reportedly ranges from 93% to 98% for patients in their 40s and is almost 100% in patients <40 years old.[8] However, because poorer adherence to eradication therapy leads to lower levels of HP eradication,[9] adherence to eradication therapy is one of the most important factors for successful HP eradication.[10] Adherence is important for both taking prescribed medications and undergoing post-eradication therapy testing. Furthermore, the success rate of

primary eradication therapy is approximately 70% to 93%.[11,12,13,14,15,16] Thus, the infection persists among the remaining approximately 7% to 30% of patients, and these patients have an increased risk of gastric cancer. An international review article indicated that various therapy-related factors influence patient adherence, such as the complexity of treatment, therapy duration, motivation of the physician, patient information, treatment efficacy, and adverse effects of treatment.[10] However, few articles published to date have reported the risk factors among Japanese patients. One study from Japan reported the proportion of and risk factors for self-interruption, which was defined as not receiving post-therapy examinations for eradication.[17] Unfortunately, the study did not detect factors associated with self-interruption other than age.[17] This was likely due to too few self-interruption events. Thus, the detailed status of adherence to eradication protocols among Japanese patients remains to be determined. To improve adherence to the eradication protocol and eventually increase the success rate of HP eradication, it is essential to determine the current incidence of self-interruption of HP eradication protocols and the risk factors associated with failure to complete treatment.

We included patients who received HP eradication therapy not in the form of a potassium-competitive acid blocker, which was released in 2016 in Japan,[18,19] but in the form of a proton pump inhibitor because of sufficient numbers of both patients who completed treatment and patients who self-interrupted treatment. The primary objective of this study was to determine the incidence of self-interruption of a HP eradication protocol. The secondary

objective was to identify factors associated with this self-interruption in Japan.

METHODS

This study is herein reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

Design

This was a retrospective cohort study with a case-control study.

Setting

The study setting was Tokyo Rinkai Hospital, a regional secondary care hospital with 400 beds located in Edogawa-ku, Tokyo, Japan.[21] The number of outpatient visits to the Department of Gastroenterology and Hepatology was 17,854 per year in 2019.[22]

Participants

Patients met the inclusion criteria if they visited the Department of Gastroenterology and Hepatology on an outpatient basis from April 2002 to September 2014 and had a positive urea breath test (UBT) result, which was defined as a value of ≥2.5‰. Patients were excluded if they

took a HP test other than a UBT or were <20 years of age. HP infection is commonly evaluated by one of the following six methods: rapid urease test, histology, culture test, UBT, anti-HP antibody assay, and fecal HP antigen assay.[23] Among these methods, we targeted patients who underwent a UBT, which is the most commonly used method for the diagnosis of HP infection in Japan.[24] This is because the UBT does not require endoscopic biopsy tissue, does not take a long time to become negative after successful treatment, and is a simple and quick method with high sensitivity and specificity.[23] Participants with a positive UBT result at the first and second visits were followed until March and September 2015, respectively. The number of participants determined the sample size.

HP eradication therapy

The HP eradication therapy protocol was as follows. At the first visit, the patient took a UBT; if the test result was positive, a physician prescribed medications for the primary eradication therapy. A post-primary eradication therapy UBT was scheduled at the first visit. At the second visit, the patient took a post-primary eradication therapy UBT; if the result was still positive, a physician prescribed medications for the secondary eradication therapy. A post-secondary eradication therapy UBT was scheduled at the second visit. The primary eradication therapy was judged to have been successful if the test result was negative. At the third visit, the patient took a post-secondary eradication therapy UBT; if the result was still positive, the secondary

eradication therapy was judged to have failed. If the result was negative, the secondary eradication therapy was judged to have been successful.

For the primary eradication therapy, amoxicillin, clarithromycin, and a proton pump inhibitor were administered for 7 days; for the secondary therapy, metronidazole was administered instead of clarithromycin.[23] The primary and secondary eradication therapies were covered by Japanese health insurance.[25]

Measurements

Outcome measure

The outcome measure was self-interruption of the eradication therapy protocol. Self-interruption was defined as failure to complete a scheduled post-eradication therapy UBT. We excluded patients who had indications for eradication therapy but did not attend a clinical visit and thus did not receive a prescription; these patients were considered highly likely to deviate from the HP eradication therapy protocol.

Potential risk factors and other variables

In addition to age and sex, we collected the following information from the electronic medical record system: whether the patient had received a medical referral letter from another hospital or clinic, whether the patient had received a recommendation following a cancer screening

result, the presence of symptoms, and the presence of any diseases requiring a UBT (atrophic gastritis, gastric and duodenal ulcers, gastric mucosa-associated lymphatic tissue lymphoma, idiopathic thrombocytopenic purpura, or post-endoscopic treatment of early gastric cancer). For the statistical analyses, age was divided into five categories: <40 years, 40 to <50 years, 50 to <60 years, 60 to <70 years, and ≥70 years.

For the primary and secondary eradication therapy, data were also collected on the results of the UBTs, the reasons for no therapeutic indication, and the reasons for no prescription.

We chose two pairs of case and control groups to compare patients who completed the post-primary and secondary eradication therapy UBTs with patients who did not. The first case group consisted of participants who did not take the post-primary eradication therapy UBT. The same number of participants was then randomly selected as the first control group of participants who took the post-primary eradication therapy UBT. Similarly, the second case group consisted of participants who did not take the post-secondary eradication therapy UBT. The same number of participants was then randomly selected as the second control group of participants who took the post-secondary eradication therapy UBT.

Statistical analyses

Descriptive analyses were performed to elucidate the following outcomes: 1) the proportion of participants who did not take the post-primary or secondary eradication therapy UBT among

participants who received a prescription for the primary or secondary eradication therapy, 2) the proportion of participants who did not take the post-primary eradication therapy UBT among participants who received a prescription for the primary eradication therapy, and 3) the proportion of participants who did not take the post-secondary eradication therapy UBT among participants who received a prescription for the secondary eradication therapy. Descriptive analyses were also performed to clarify the reasons for no indication and no prescription. Missing values were described as “unknown.”

In the case-control study, we used multiple logistic analyses to identify the factors that were associated with failure to take the post-eradication therapy UBT, including age category, sex (female/male = 0/1), presence of a medical referral letter from another hospital or clinic (not present/present = 0/1), whether a patient received a recommendation following a cancer screening result (no/yes = 0/1), presence of symptoms (not present/present = 0/1), and an indicator variable of a disease requiring a UBT (atrophic gastritis, gastric and duodenal ulcers, gastric mucosa-associated lymphatic tissue lymphoma, idiopathic thrombocytopenic purpura, post-endoscopic treatment of early gastric cancer, and other diseases). We excluded patients with malignant tumors who received a prescription for eradication therapy but did not take the post-primary eradication therapy UBT from the multiple logistic regression analyses because they did not self-interrupt, but instead deviated from, the HP eradication therapy protocol.

STATA/MP version 15.1 (StataCorp, College Station, TX) was used for the statistical

analyses, and p-values of <0.05 were considered statistically significant.

Ethical considerations

This study was approved by the Ethics Committee of Tokyo Rinkai Hospital (reception number: 168) and by the Ethics Committee of The Jikei University School of Medicine (approval number: 29-295(8911)). It was conducted in accordance with the Declaration of Helsinki[26] and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.[27] We did not obtain individual patients' informed consent. However, we displayed posters in the hospital that provided possible participants with information about the collection and use of their data for this study and guaranteed them protection of personal information and opportunities for refusal.

RESULTS

From April 2002 to September 2014, 3,518 patients visited the Department of Gastroenterology and Hepatology on an outpatient basis for suspected HP infection. Among them, 97 patients took a HP test other than a UBT: 86 took an anti-HP antibody assay, 8 took a fecal HP antigen assay, and 3 underwent a histological examination. Thirteen patients aged <20 years were excluded. Thus, 3,408 patients took the UBT, and 2,488 patients with a positive UBT result

were included (Figure 1). Among them, 238 and 32 patients failed to take the post-primary and secondary eradication therapy UBTs (self-interruption of the primary and secondary eradication therapy protocol), respectively (Figures 1 and 2). In total, 270 patients self-interrupted the protocol.

Figure 1.

Figure 2.

The characteristics of the study participants are shown in Table 1.

Table 1.

Descriptive analyses showed that the proportion of participants who did not take the post-primary or secondary eradication therapy UBT among participants who received a prescription for the primary or secondary eradication therapy was 9.6%. We also found that the proportion of participants who did not take the post-primary eradication therapy UBT among participants who received a prescription for the primary eradication therapy was 10.0%, and the proportion of participants who did not take the post-secondary eradication therapy UBT among participants who received a prescription for the secondary eradication therapy was 7.4%.

The reasons for no indication and no prescription are shown in Table 2. Among 113 patients who had an indication for eradication therapy but did not receive a prescription, 27 (23.9%) did not attend a clinical visit to receive the prescription.

Table 2.

The characteristics of patients who received a prescription for HP primary and secondary eradication therapy are shown in Table 1. Among these patients, we chose two pairs of case and control groups to compare patients who completed the post-primary and secondary eradication therapy UBTs with patients who did not. Multiple logistic regression analyses using the first case and control groups showed that the presence of gastric and duodenal ulcers (compared with atrophic gastritis) was associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 2.220, p = 0.001) (Table 3). An age of ≥50 years (compared with <40 years) was less strongly associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 0.467, 0.307, and 0.185 and p = 0.011, <0.001, and <0.001 for age of 50 to <60 years, 60 to <70 years, and ≥70 years, respectively) (Table 3). Receiving a recommendation following a cancer screening result was also less strongly associated with failure to take the post-eradication therapy UBT (adjusted odds ratio = 0.249, p = 0.001) (Table 3).

Although the associated risk factors might have differed between the first and second case and control groups, we were unable to perform the analysis using solely the second case and control groups because of too few cases of self-interruption. However, we did perform multiple logistic regression analyses using the combined first and second case and control groups. The results of this analysis were similar to those of the first case and control groups (Table 4).

In these analyses, there were no missing values, and three patients with malignant tumors were excluded from the first case group.

Table 3.

Table 4.

DISCUSSION

Approximately 10% of the study participants self-interrupted the HP eradication protocol. Additionally, age <40 years (compared with ≥50 years) and the presence of gastric and duodenal ulcers (compared with atrophic gastritis) were risk factors for poor adherence. Furthermore, receiving a recommendation following a cancer screening result was associated with good adherence.

Approximately 10% the study participants self-interrupted, whereas a previous retrospective cohort study in Japan reported a proportion of 6.0%.[17] The proportion of patients aged <50 years (36.6%) in this study was higher than the proportion in the previous study (23.6%).[17] As found in both the previous study[17] and the present study, younger age was associated with poor adherence, which presumably led to the higher proportion of self-interruption in this study. In this study setting and period, the eradication therapy mainly included lansoprazole as the proton pump inhibitor. The success rate of primary and secondary eradication therapy with lansoprazole ranges from 83.7% to 91.1%[11] and from 84.8% to 93.4%,[28,29] respectively. Thus, eradication therapy failed in the remaining at least 8.9% and

6.6% of patients who received HP primary and secondary eradication therapy, respectively. Similarly, eradication therapy also likely failed among participants who self-interrupted the protocol (238 and 32 patients undergoing primary and secondary eradication therapy, respectively). However, we believe that the rate of successful eradication was lower because fewer participants among those who self-interrupted presumably took their medications in the appropriate manner than those who completed the eradication therapy protocol.

In 2014, 7,168,070 HP primary eradication packs were prescribed to outpatients (in-hospital and external prescriptions)[30,31]: 3,966,587 prescriptions of Lansap® 400/800 (containing lansoprazole 60 mg/day, amoxicillin 1500 mg/day, and clarithromycin 400/800 mg/day)[32] and 3,201,483 prescriptions of Rabecure® pack 400/800 (containing rabeprazole 20 mg/day, amoxicillin 1500 mg/day, and clarithromycin 400/800 mg/day).[33] The treatment duration is 7 days; thus, the estimated number of outpatients who took HP primary eradication therapy was 1,024,010 patients: 566,655 and 457,355 outpatients received Lansap® 400/800 and Rabecure® pack 400/800, respectively. If the self-interruption rate in this study and the success rate of primary eradication therapy with lansoprazole (83.7%–91.1%[11]) and rabeprazole (85.7%–89.0%[13]) are applied to the estimated number of outpatients, HP infection would persist among at least 10,049 patients. Gastric cancer reportedly developed in 2.9% of HP-infected patients during a follow-up period of 7.6 years,[34] which would lead to 291 patients developing gastric cancer during the same period. With HP secondary eradication therapy and individually

prescribed medications (not pack prescriptions), more patients would develop gastric cancer. Therefore, it is important to reduce the incidence of self-interruption from a public health perspective.

Age <40 years was associated with poor adherence, which is similar to the results of a previous study conducted in Japan.[17] That study identified younger age (30–49 years) as a factor associated with self-interruption, although the study included a considerably smaller number of self-interruption events.[17] Likewise, younger age is a common risk factor for poor adherence among several other diseases.[35,36,37] The preventive effect of HP eradication therapy in reducing the incidence of gastric cancer was reported to be almost 100% in patients <40 years old.[8] Thus, patients who would receive the greatest benefit from eradication therapy often fail to complete their treatment. Additionally, gastric and duodenal ulcers were associated with poor adherence in the present study. Asymptomatic disease is expected to be a major predictor of poor adherence to medication.[38] Disappearance of symptoms achieved by the treatment might result in self-interruption. This is the first study in Japan to identify the association between poor adherence to eradication therapy and the presence of gastric and duodenal ulcers. Further studies are required to clarify this relationship in more detail. Moreover, we observed good adherence in patients who had received a recommendation following a cancer screening result, which might reflect patients' greater awareness of their health.

Among other diseases and treatments, such as antiretroviral therapy for the treatment

of human immunodeficiency virus (HIV) infection and direct-acting antivirals for the treatment of hepatitis C virus (HCV) infection, various approaches have been proposed to prevent self-interruption and increase adherence.[39,40] In patients with HIV or HCV infection, for example, health care professionals are encouraged to explain the expected adverse effects of treatment, promote patients' understanding of the significance of treatment, and emphasize the importance of adherence. Clinicians are also encouraged to deliver the treatments with the cooperation of a multidisciplinary health care team, including physicians, nurses, pharmacists, and other health care professionals. Similarly, to increase adherence to HP eradication therapy, it is considered important to promote patients' understanding of the treatments and deliver the treatments with the cooperation of a multidisciplinary health care team. It might also be important for local governments or medical institutions to establish follow-up systems, as has been conducted for hepatitis B and C virus infections in some areas in Japan.[41]

In Japan, Vonosap® pack 400/800 and Vonopion® pack, which include the potassium-competitive acid blocker vonoprazan, were released in 2016.[18,19] Because of their higher eradication rate,[16] they have become the main drugs for HP eradication therapy. However, the results and findings of the present study, which was conducted before Vonosap® pack 400/800 and Vonopion® pack became available, are still considered important. For example, the number of doses per day (two), the number of tablets or capsules taken per day (10 or 12), and the treatment duration (7 days) are identical between Lansap®/Rabecure® pack 400/800 and

Vonosap® pack 400/800.[18,32,33] Additionally, the incidence of adverse events during HP primary eradication therapy is reportedly comparable between vonoprazan and lansoprazole.[16] The pharmaceutical prices of Lansap®/Rabecure® pack 400/800 and Vonosap® pack 400/800 are also comparable.[42] Considering these factors, which are assumed to influence adherence to treatment,[10] the proportion of self-interruption of the HP eradication protocol with Vonosap® pack 400/800 and Vonopion® pack would probably be the same as the proportion found in this study. Therefore, the results of this study will provide the basis for future research regarding potassium-competitive acid blockers; such research is warranted to more accurately assess the current incidence of self-interruption.

This study has several limitations. First, self-interruption was defined as failure to complete a scheduled post-eradication therapy UBT. The patients who self-interrupted were not followed up and might have taken a post-eradication therapy UBT at another medical institution. In this case, the proportion of self-interruption would have been overestimated. Second, this was a retrospective cohort study. Information about the potential risk factors was collected from the electronic medical record system; as a consequence, all covariables that should have been adjusted were not collected because of limited sources. Therefore, other factors might have influenced self-interruption. Third, we did not include patients who had indications for eradication therapy but did not attend a clinical visit and thus did not receive a prescription. Exclusion of these patients, who might have had different factors associated with self-

interruption, could have resulted in overestimation or underestimation of our data; however, the influence of this small number of patients was presumably limited. Finally, this study was conducted at a single medical institution, which limits the generalizability of the results to some extent. A multicenter study is warranted to ensure greater generalizability.

CONCLUSION

Approximately 10% of the study participants self-interrupted the HP eradication protocol. Additionally, age <40 years and the presence of gastric and duodenal ulcers were risk factors for poor adherence.

Conflict of Interest Statement

This study was supported by The Jikei University Research Fund for Graduate Students (grant number: N/A). The funder played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. MM received lecture fees and lecture travel fees from the Centre for Family Medicine Development of the Japanese Health and Welfare Co-operative Federation. MM is an adviser for the Centre for Family Medicine Development Practice-Based Research

Network and a program director of the Jikei Clinical Research Program for Primary-care. MM's son-in-law works at IQVIA Services Japan K.K., which is a contract research organization and a contract sales organization. All other authors declare no competing interests.

Authors' contributions

HI designed the study, collected and interpreted the data, and prepared and reviewed the manuscript. YS designed the study, analyzed and interpreted the data, and prepared and reviewed the manuscript. RM designed the study, interpreted the data, and prepared and reviewed the manuscript. TY contributed to the collection of the data and review of the manuscript. HW, YN, SY, TH, and SM contributed to the design of the study and review of the manuscript. MM contributed to the design of the study, interpretation of the data, and preparation and review of the manuscript. All authors read and approved the final manuscript for submission.

REFERENCES

1. International Agency for Research on Cancer, World Health Organization. Stomach. 2020. http://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf. [accessed 2021-03-03]
2. Thrumurthy SG, Chaudry MA, Hochhauser D, Mughal M. The diagnosis and management of gastric cancer. BMJ. 2013;347:f6367.
3. International Agency for Research on Cancer, World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: schistosomes, liver flakes and *Helicobacter pylori*. 1994. https://publications.iarc.fr/_publications/media/download/2041/5c102d23efdf6b74fe03ce47ce92a82f28bd95d8.pdf. [accessed 2021-03-03]
4. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. Am J Gastroenterol. 2017;112:212–39.
5. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology. 2017;153:420–9.
6. World Cancer Research Fund International. Stomach cancer statistics. 2018. https://www.wcrf.org/dietandcancer/cancer-trends/stomach-cancer-statistics. [accessed 2021-03-03]

7. Asaka M, Mabe K. Strategies for eliminating death from gastric cancer in Japan. Proc Jpn Acad Ser B Phys Biol. 2014;90:251–8.

8. Asaka M, Kato M, Graham DY. Strategy for eliminating gastric cancer in Japan. Helicobacter. 2010;15:486–90.

9. Graham DY, Lew GM, Malaty HM, Evans DG, Evans Jr DJ, Klein PD, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology. 1992;102:493–6.

10. O'Connor JPA, Taneike I, O'Morain C. Improving adherence with *Helicobacter pylori* eradication therapy: when and how? Therap Adv Gastroenterol. 2009;2:273–9.

11. Asaka M, Sugiyama T, Kato M, Satoh K, Kuwayama H, Fukuda Y, et al. A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in Japanese peptic ulcer patients. Helicobacter. 2001;6:254–61.

12. Kuwayama H, Luk G, Yoshida S, Nakamura T, Kubo M, Uemura N, et al. Efficacy of a low-dose omeprazole-based triple-therapy regimen for *Helicobacter pylori* eradication independent of cytochrome P450 Genotype: the Japanese MACH Study. Clin Drug Investig. 2005;25:293–305.

13. Kuwayama H, Asaka M, Sugiyama T, Fukuda Y, Aoyama N, Hirai Y, et al. Rabeprazole-based eradication therapy for *Helicobacter pylori*: a large-scale study in Japan. Aliment Pharmacol Ther. 2007;25:1105–13.

14. Nishida T, Tsujii M, Tanimura H, Tsutsui S, Tsuji S, Takeda A, et al. Comparative study of esomeprazole and lansoprazole in triple therapy for eradication of *Helicobacter pylori* in Japan. World J Gastroenterol. 2014;20:4362–9.

15. Saito Y, Serizawa H, Kato Y, Nakano M, Nakamura M, Saito H, et al. First-line eradication for *Helicobacter pylori*-positive gastritis by esomeprazole-based triple therapy is influenced by CYP2C19 genotype. World J Gastroenterol. 2015;21:13548–54.

16. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. Gut. 2016;65:1439–46.

17. Yokota N, Ae R, Amenomori M, Kitagawa K, Nakamura T, Yokota T, et al. Clinical background factors affecting outcomes of *Helicobacter pylori* eradication therapy in primary care. J Gen Fam Med. 2019;20:139–45.

18. Takeda Pharmaceutical Company Limited. Vonosap® pack 400/800. 2020. https://s3-ap-northeast-1.amazonaws.com/medley-

medicine/prescriptionpdf/400256_6199104X1023_1_10.pdf. [accessed 2021-03-03] [in Japanese]

19. Takeda Pharmaceutical Company Limited. Vonopion® pack. 2020. https://s3-ap-northeast-1.amazonaws.com/medley-medicine/prescriptionpdf/400256_6199105X1028_1_12.pdf. [accessed 2021-03-03] [in Japanese]
20. Equator network. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. https://www.equator-network.org/reporting-guidelines/strobe. [accessed 2021-03-03]
21. Tokyo Rinkai Hospital. Hospital overview. 2019. http://www.tokyorinkai.jp/hospital/overview.html. [accessed 2021-03-03] [in Japanese]
22. Tokyo Rinkai Hospital. Gastroenterology & Hepatology. 2019. http://www.tokyorinkai.jp/shinryoka/02.html. [accessed 2021-03-03] [in Japanese]
23. Kato M, Ota H, Okuda M, Kikuchi S, Satoh K, Shimoyama T, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2016 revised edition. Helicobacter. 2019;24:e12597

24. Ministry of Health, Labour and Welfare. 5th NDB open data: D examination. 2020. https://www.mhlw.go.jp/content/12400000/000539670.xlsx. [accessed 2021-03-03] [in Japanese]

25. Ministry of Health, Labour and Welfare. Partial revision of "diagnosis and treatment of *Helicobacter pylori* Infection". 2013. https://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/iryouhoken15/dl/tuuchi-h24-0221-31.pdf. [accessed 2021-03-03] [in Japanese]

26. World Medical Association. Declaration of Helsinki. 2021. https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki. [accessed 2021-03-03]

27. Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects. 2017. https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153339.pdf. [accessed 2021-03-03] [in Japanese]

28. Asaoka D, Nagahara A, Matsuhisa T, Takahashi S, Tokunaga K, Kawai T, et al. Trends of second-line eradication therapy for *Helicobacter pylori* in Japan: a multicenter study in the Tokyo metropolitan area. Helicobacter. 2013;18:468–72.

29. Matsuhisa T, Kawai T, Masaoka T, Suzuki H, Ito M, Kawamura Y, et al. Efficacy of metronidazole as second-line drug for the treatment of *Helicobacter pylori* infection

in the Japanese population: a multicenter study in the Tokyo metropolitan area. Helicobacter. 2006;11:152–8.

30. Ministry of Health, Labour and Welfare. The first NDB open data: Medication, outpatient (in-hospital prescription). 2020. https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000139841.xlsx. [accessed 2021-03-03] [in Japanese]
31. Ministry of Health, Labour and Welfare. The first NDB open data: Medication, outpatient (external prescription). 2020. https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000139843.xlsx. [accessed 2021-03-03] [in Japanese]
32. Takeda Pharmaceutical Company Limited. Lansap® 400/800. 2018. https://s3-ap-northeast-1.amazonaws.com/medley-medicine/prescriptionpdf/400256_6199100X1025_1_29.pdf. [accessed 2021-03-03] [in Japanese]
33. Eisai Co., Ltd. Rabecure® pack 400/800. 2019. https://s3-ap-northeast-1.amazonaws.com/medley-medicine/prescriptionpdf/170033_6199102X1024_1_12.pdf. [accessed 2021-03-03] [in Japanese]

34. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.

35. Greer JA, Amoyal N, Nisotel L, Fishbein JN, MacDonald J, Stagl J, et al. A systematic review of adherence to oral antineoplastic therapies. Oncologist. 2016;21: 354–76.

36. Center for Disease Control and Prevention. HIV and Youth. 2020. https://www.cdc.gov/hiv/group/age/youth/index.html. [accessed 2021-03-03]

37. Burnier M, Egan BM. Adherence in hypertension. Circ Res. 2019;124:1124–40.

38. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.

39. Panel on Antiretroviral Guidelines for Adults and Adolescents, Department of Health and Human Service. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2019. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. [accessed 2021-03-03]

40. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69:461–511.

41. National Institute of Infectious Diseases. Infectious Agents Surveillance Report: follow-up system for hepatitis virus screening positive patients in Ishikawa

Prefecture. 2021. https://www.niid.go.jp/niid/ja/typhi-m/iasr-reference/2535-related-articles/related-articles-491/10128-491r03.html. [accessed 2021-03-03] [in Japanese]

42. Nikkei Medical. Prescription drug dictionary. https://medical.nikkeibp.co.jp/inc/all/drugdic. [accessed 2021-03-03] [in Japanese]

Figure Legends

Figure 1. Flow diagram detailing number of patients in each step of HP primary eradication therapy

HP, *Helicobacter pylori*; UBT, urea breath test.

Figure 2. Flow diagram detailing number of patients in each step of HP secondary eradication therapy

HP, *Helicobacter pylori*; UBT, urea breath test.

Table 1. Characteristics of study participants and patients who received a prescription for HP eradication therapy

HP, *Helicobacter pylori*; SD, standard deviation.

Table 2. Reasons for no indication and no prescription

Table 3. Multiple logistic regression analyses of patients who failed to take post-primary eradication therapy UBT

UBT, urea breath test; OR, odds ratio; CI, confidence interval.

Table 4. Multiple logistic regression analyses of patients who failed to take post-primary and secondary eradication therapy UBTs

UBT, urea breath test; OR, odds ratio; CI, confidence interval.

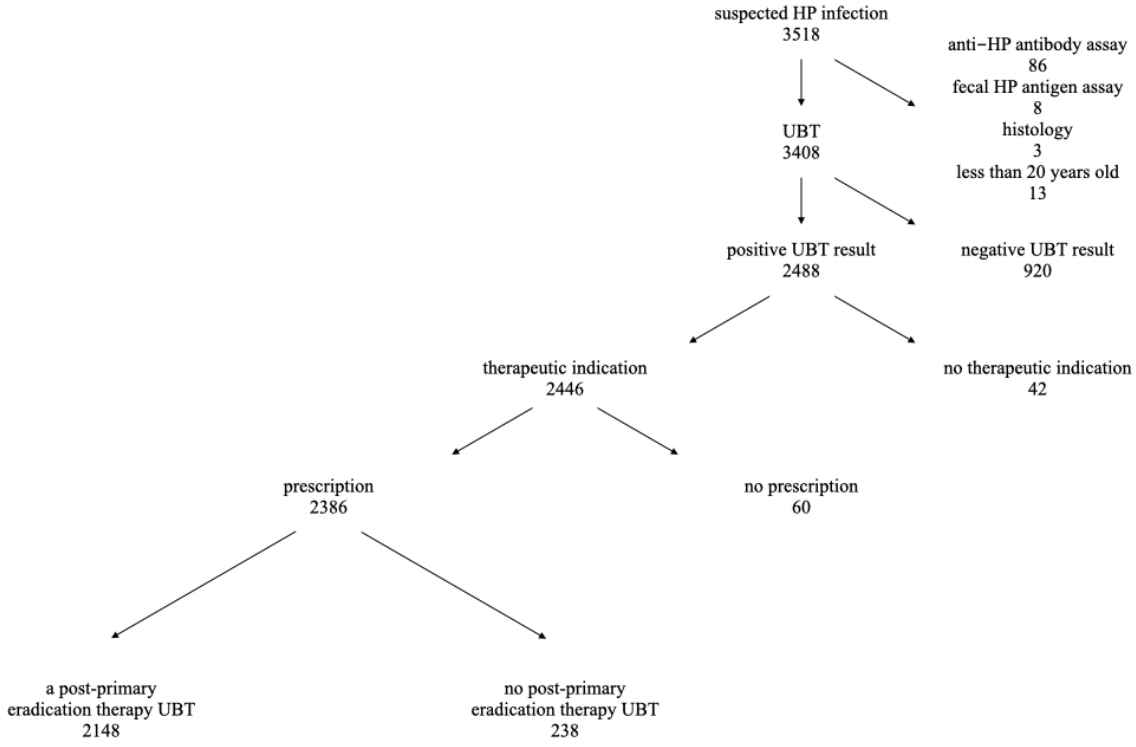

Figure 1. Flow diagram detailing number of patients in each step of HP primary eradication therapy

HP, *Helicobacter pylori*; UBT, urea breath test.

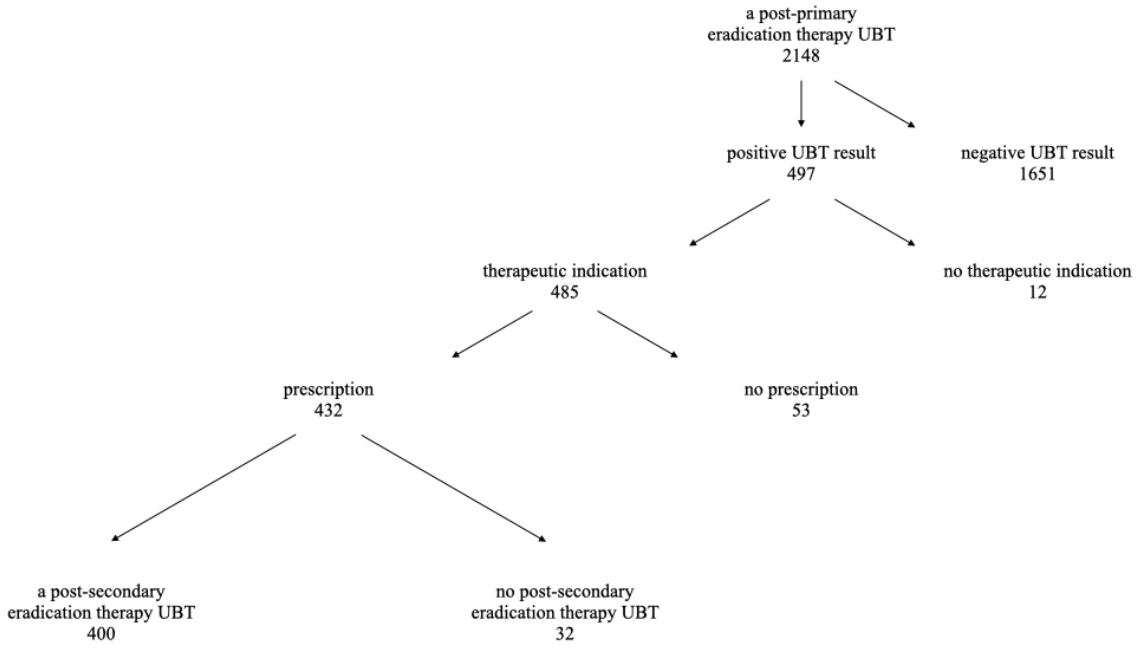

Figure 2. Flow diagram detailing number of patients in each step of HP secondary eradication therapy

HP, *Helicobacter pylori*; UBT, urea breath test.

Table 1. Characteristics of study participants and patients who received a prescription for HP eradication therapy

	Study participants (n = 2,488)	Patients who received a prescription for HP primary eradication therapy (n = 2,386)	Patients who received a prescription for HP secondary eradication therapy (n = 432)
Age, mean (SD), years	54.0 (12.9)	54.2 (12.8)	53.6 (13.4)
By age group, No. (%)			
< 40 years	353 (14.2)	337 (14.1)	66 (15.3)
40 to < 50 years	558 (22.4)	524 (22.0)	108 (25.0)
50 to < 60 years	653 (26.3)	643 (27.0)	95 (22.0)
60 to < 70 years	626 (25.2)	594 (24.9)	103 (23.8)
≥ 70 years	298 (12.0)	288 (12.1)	60 (13.9)
Sex, No. (%)			
Female	1,030 (41.4)	986 (41.3)	197 (45.6)
Male	1,458 (58.6)	1,400 (58.7)	235 (54.4)

HP, *Helicobacter pylori*; SD, standard deviation.

Table 2. Reasons for no indication and no prescription

No indication	No. (%)
Allergy	15 (27.8)
Drug resistance	5 (9.3)
Kidney or liver dysfunction	5 (9.3)
Stomach cancer	13 (24.1)
Under treatment for other diseases	7 (13.0)
Other	6 (11.1)
Unknown	3 (5.6)
Total	54 (100.0)
No prescription	No. (%)
No clinical visit	27 (23.9)
No request for treatment	25 (22.1)
Under treatment for other diseases	9 (8.0)
Treatment at another medical institution	6 (5.3)
Before insurance coverage	42 (37.2)
Other	3 (2.7)
Unknown	1 (0.9)
Total	113 (100.0)

Table 3. Multiple logistic regression analyses of patients who failed to take post-primary eradication therapy UBT

Explanatory variables	Crude OR	P-value	95% CI	Adjusted OR	P-value	95% CI
Age						
< 40 years	Reference			Reference		
40 to < 50 years	0.573	0.059	0.322–1.021	0.618	0.120	0.337–1.133
50 to < 60 years	0.469	0.008	0.268–0.820	0.467	0.011	0.259–0.841
60 to < 70 years	0.280	< 0.001	0.154–0.507	0.307	< 0.001	0.165–0.570
≥ 70 years	0.230	< 0.001	0.108–0.490	0.185	< 0.001	0.082–0.418
Sex						
Female	Reference			Reference		
Male	1.261	0.239	0.857–1.856	0.943	0.785	0.617–1.441
Presence of a medical referral letter						
Without a medical referral letter	Reference			Reference		
With a medical referral letter	0.627	0.024	0.417–0.942	1.127	0.639	0.683–1.860
Cancer screening						
No cancer screening	Reference			Reference		
After cancer screening	0.388	< 0.001	0.247–0.611	0.249	0.001	0.108–0.573
Presence of symptoms						
Without symptoms	Reference			Reference		
With symptoms	1.622	0.039	1.025–2.567	0.476	0.078	0.208–1.086
Presence of diseases which require taking UBT						
Atrophic gastritis	Reference			Reference		
Gastric and duodenal ulcer	2.619	< 0.001	1.703–4.029	2.220	0.001	1.373–3.589

Gastric mucosa-associated lymphatic tissue lymphoma	—	—	—	—	—	—
Idiopathic thrombocytopenic purpura	—	—	—	—	—	—
After endoscopic treatment of early gastric cancer	4.146	0.251	0.365–47.061	5.033	0.222	0.377–67.203
Other diseases	6.220	0.118	0.628–61.642	4.206	0.234	0.396–44.702

UBT, urea breath test; OR, odds ratio; CI, confidence interval.

Table 4. Multiple logistic regression analyses of patients who failed to take post-primary and secondary eradication therapy UBTs

Explanatory variables	Crude OR	P-value	95% CI	Adjusted OR	P-value	95% CI
Age						
< 40 years	Reference			Reference		
40 to < 50 years	0.523	0.018	0.305–0.897	0.607	0.087	0.343–1.075
50 to < 60 years	0.426	0.002	0.250–0.727	0.431	0.003	0.246–0.756
60 to < 70 years	0.251	< 0.001	0.143–0.442	0.282	< 0.001	0.157–0.509
≥ 70 years	0.246	< 0.001	0.126–0.483	0.212	< 0.001	0.103–0.436
Sex						
Female	Reference			Reference		
Male	1.306	0.144	0.912–1.870	0.971	0.884	0.653–1.444
Presence of a medical referral letter						
Without a medical referral letter	Reference			Reference		
With a medical referral letter	0.678	0.050	0.459–0.999	1.179	0.497	0.733–1.899
Cancer screening						
No cancer screening	Reference			Reference		
After cancer screening	0.355	< 0.001	0.231–0.546	0.220	< 0.001	0.102–0.475
Presence of symptoms						
Without symptoms	Reference			Reference		
With symptoms	1.716	0.016	1.105–2.665	0.461	0.054	0.209–1.015
Presence of diseases which require taking UBT						
Atrophic gastritis	Reference			Reference		
Gastric and duodenal ulcer	2.808	< 0.001	1.879–4.196	2.278	< 0.001	1.457–3.563

Gastric mucosa-associated lymphatic tissue lymphoma	—	—	—	—	—	—
Idiopathic thrombocytopenic purpura	2.149	0.591	0.132–35.104	1.239	0.882	0.073–20.973
After endoscopic treatment of early gastric cancer	4.298	0.239	0.380–48.589	4.019	0.286	0.312–51.837
Other diseases	6.447	0.111	0.653–63.629	4.222	0.232	0.397–44.867

UBT, urea breath test; OR, odds ratio; CI, confidence interval.