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Self-interruption of *Helicobacter pylori* Eradication Therapy and its Associated Risk Factors

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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 in Tokyo.

Subjects : The subjects were outpatients 20 years or older of the Department of Gastroenterology and Hepatology from April 2002 through September 2014 with positive results of a urea breath test (UBT) for *HP*.

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

Results : Of 2,488 patients, 270 had self-interrupted. Associated with self-interruption was the presence of gastric and duodenal ulcers (adjusted odds ratio = 2.220, $p = 0.001$). An age of ≥ 50 years was less strongly associated with self-interruption than was an age < 40 years (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). Self-interruption was less likely if the patient had received a recommendation following a cancer screening result (adjusted odds ratio = 0.249, $p = 0.001$).

Conclusion : Approximately 10% of patients failed to undergo a scheduled post-eradication therapy UBT for *HP*. Risk factors for poor adherence were age < 40 years and the presence of gastric and duodenal ulcers.

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Key words : *Helicobacter pylori*, eradication therapy, self-interruption, risk factors

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INTRODUCTION

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

Nevertheless, approximately 4.4 billion people 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 the treatment of chronic *HP* gastritis in 2013[7].

The effect of *HP* eradication therapy on reducing the incidence of gastric cancer reportedly ranges from 93% to 98% for patients aged 40 to 49 years and is almost 100% in patients younger than 40 years[8]. However, because poorer adherence to eradication therapy decreases the effectiveness of *HP* eradication[9], adherence to therapy is an important factor for successful *HP* eradication[10]. Adherence is important for both taking prescribed medications and undergoing post-eradication therapy testing. Furthermore, reported success rates of primary eradication therapy range from 70% to 93%[11–16]. Thus, despite eradication therapy, *HP* infection would persist in 7% to 30% of patients, who would have an increased risk of gastric cancer. An international review article indicated that patient adherence to eradication therapy is affected by various factors, such as the motivation of physicians ; the information given to patients ; and the complexity, duration, efficacy, and adverse effects of treatment[10]. However, few articles have reported the risk factors for poor adherence among Japanese patients. One study of Japanese patients has examined the frequency of and risk factors for self-interruption, which was defined as not undergoing posttherapy examinations for eradication[17]. Unfortunately, the only factor associated with self-interruption detected by this study was age[17], possibly owing to the few self-interruption events. Thus, how well Japanese patients adhere to eradication protocols remains to be determined. To increase both the adherence rate and, eventually, the success rate of *HP* eradication protocols, it is essential to determine the current incidence of protocol self-interruption by patients and risk factors associated with a failure to complete treatment.

Therefore, with a primary objective of determining the incidence of self-interruption of a *HP* eradication protocol and a secondary objective of identifying factors associated with this self-interruption in Japan, we performed the present retrospective study in which showed the reality of patients' behavior. Included in this study were patients who had received *HP* eradication therapy, not in the form of a potassium-competitive acid blocker that was released in 2016 in Japan[18,19], but in the form of a proton pump inhibitor because of the sufficient numbers of both patients who had completed treatment and patients who had self-interrupted treatment.

METHODS

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

Design

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

Setting

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

Subjects

Patients met the inclusion criteria of this study if they had visited the Department of Gastroenterology and Hepatology as an outpatient from April 2002 through September 2014 and had a result of an urea breath test (UBT) which was positive, defined as a value of ≥ 2.5. Patients were excluded if they had undergone a *HP* test other than a UBT or were younger than 20 years. The *HP* infection is commonly

evaluated by 1 of the following 6 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 a successful treatment, and is a simple and quick method with high sensitivity and specificity[23]. Patients were followed up owing to a positive UBT result after the first visit until March 2015 and after a second visits until September 2015. The number of subjects determined the sample size.

HP eradication therapy

The *HP* eradication therapy protocol was as follows. At the first visit, the patient underwent a UBT ; if the result was positive, a physician prescribed medications for the primary eradication therapy and scheduled a post-primary eradication therapy UBT. At the second visit, the patient again underwent a UBT ; if the result was positive, a physician prescribed medications for the secondary eradication therapy and scheduled a post-secondary eradication therapy UBT. The primary eradication therapy was judged to have been successful if the post-primary eradication therapy UBT was negative. At the third visit, the patient underwent a post-secondary eradication therapy UBT ; if the result was again positive, the secondary eradication therapy was judged to have failed. If the UBT 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 undergo a scheduled post-eradication therapy UBT. Patients were excluded if they had 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 have deviated from the *HP* eradication therapy protocol.

Potential risk factors and other variables

In addition to age and sex, the following information was collected 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 postendoscopic treatment of early gastric cancer). For the statistical analyses, age was divided into 5 categories : < 40 years, 40 to < 50 years, 50 to < 60 years, 60 to < 70 years, and ≥ 70 years.

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

We chose 2 pairs of case and control groups to compare patients who completed the post-primary and post-secondary eradication therapy UBTs with patients who did not. The first case group consisted of subjects who had not undergone the post-primary eradication therapy UBT. The first control group was the same number of randomly selected subjects who had undergone the post-primary eradication therapy UBT. Similarly, the second case group consisted of subjects who had not undergone the post-secondary eradication therapy UBT. The second control group was the same number of randomly selected subjects who had undergone the post-secondary eradication therapy UBT.

Statistical analyses

Descriptive analyses were performed to elucidate the following outcomes : (1) the proportion of subjects who did not undergo the post-primary or post-secondary eradication therapy UBT among subjects who had received a prescription for the primary or secondary eradication therapy, (2) the proportion of subjects who did not undergo the post-primary eradication therapy UBT among subjects who had received a prescription for the primary eradication therapy,

and (3) the proportion of subjects who did not undergo the post-secondary eradication therapy UBT among subjects who had 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 undergo 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 had 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, postendoscopic treatment of early gastric cancer, and other diseases). We excluded patients who had malignant tumors and had received a prescription for eradication therapy but did not undergo 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.

The program STATA/MP version 15.1 (StataCorp, College Station, TX, USA) 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)). The study 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 informed consent from individual patients. However, we displayed posters in the hospital that provided possible subjects 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 through September 2014, 3,518 patients suspected to have *HP* infection visited the Department of Gastroenterology and Hepatology on an outpatient basis. Among them, 97 patients underwent a *HP* test other than a UBT, which was an anti-*HP* antibody assay for 86 patients, a fecal *HP* antigen assay for 8 patients, and a histological examination for 3 patients. Thirteen patients younger than 20 years were excluded. Thus, 3,408 patients underwent the UBT, and 2,488 patients who had positive results were included as subjects (Table 1, Fig. 1). Of these 2,488 patients, 238 failed to undergo the post-primary eradication therapy UBT (Fig. 1) and 32 patients failed to undergo the post-secondary eradication therapy UBT (Fig. 2).

Table 1. Characteristics of study participants and patients who received a prescription for *Helicobacter pylori* 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, number (%)			
< 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, number (%)			
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.

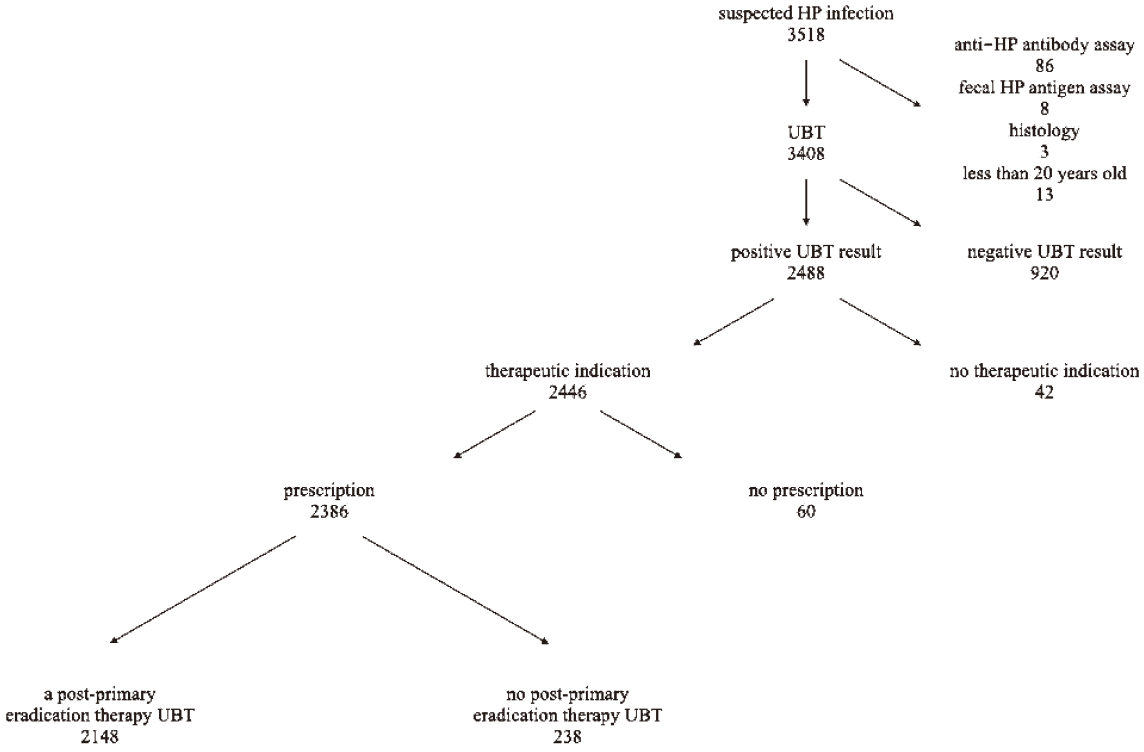

Fig. 1. Flow diagram detailing the number of patients in each step of *Helicobacter pylori* primary eradication therapy
HP, *Helicobacter pylori* ; UBT, urea breath test.

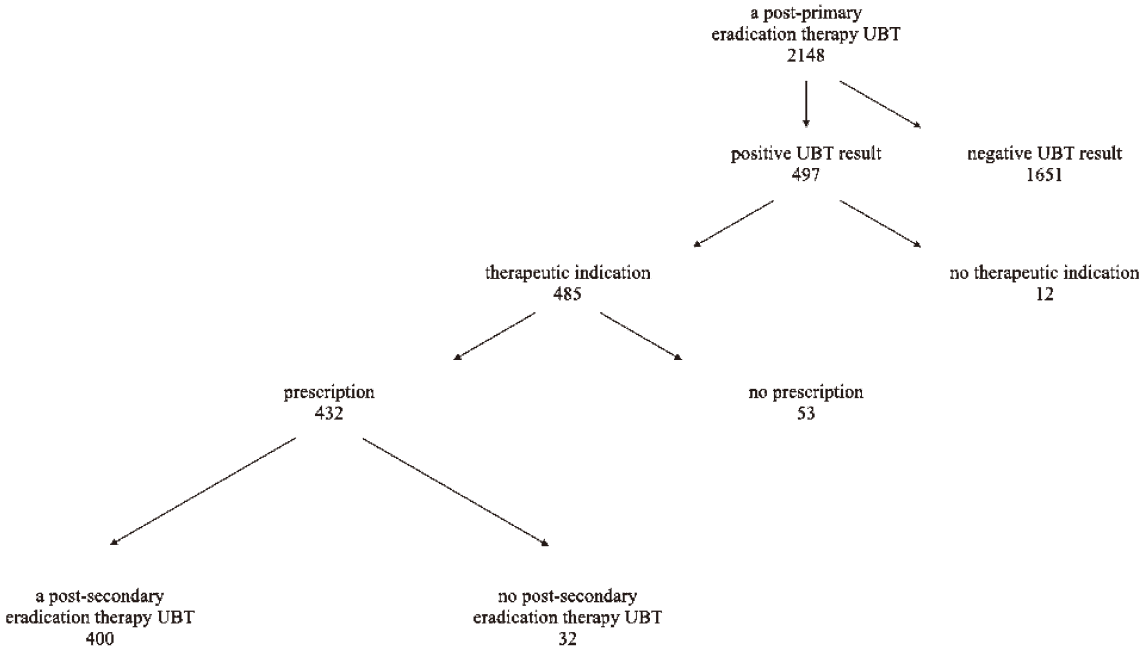

Fig. 2. Flow diagram detailing number of patients in each step of *Helicobacter pylori* secondary eradication therapy
HP, *Helicobacter pylori* ; UBT, urea breath test.

Therefore, a total of 270 patients self-interrupted the primary or secondary eradication therapy protocol.

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

Of the 113 patients who had an indication for eradication therapy, 27 (23.9%) did not receive a prescription because they had not made the necessary clinic visit (Table 2).

Multiple logistic regression analyses of patients who did or did not undergo the post-primary eradication therapy

Table 2. Reasons for no indication and no prescription

No indication	Number (%)
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 urea breath test

Explanatory variables	Crude odds ratio	*P*-value	95% CI	Adjusted odds ratio	*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 urea breath test						
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 post-secondary eradication therapy urea breath tests

Explanatory variables	Crude odds ratio	*P*-value	95% CI	Adjusted odds ratio	*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 undergoing urea breath test						
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.

UBT showed that a failure to undergo the post-eradication therapy UBT was positively associated with the presence of gastric and duodenal ulcers compared to atrophic gastritis as a reference (Table 3). This failure to undergo the post-eradication therapy UBT was less strongly associated with an age of 50 years or older than with an age of younger than 40 years. Furthermore, failure to undergo the post-eradication therapy UBT was also less strongly associated with the patient receiving a recommendation after a cancer-screening result.

Although the associated risk factors might have differed between the first and second case and control groups, we were unable to perform the analysis with only patients after the secondary eradication therapy because too few of these patients had performed self-interruption and did not undergone UBT. However, multiple logistic regression analyses of the combined first and second case groups and each control groups (Table 3) had results similar to those of the first case and its control groups (Table 4). In these analyses, no values were missing, and 3 patients with malignant tumors were excluded from the first case group.

Discussion

The present study has found that self-interruption of the *HP* eradication protocol, defined as not undergoing a scheduled UBT after receiving eradication therapy, was performed by approximately 10% of the patients. In addition, risk factors for poor adherence to the protocol were age < 40 years (versus an age ≥ 50 years) and the presence of gastric and duodenal ulcers (versus the presence of atrophic gastritis). Furthermore, associated with good adherence to the protocol was the patient having received a recommendation following a cancer screening result.

In the present study approximately 10% of patients self-interrupted, whereas a previous retrospective cohort

study in Japan has found that 6.0% of patients had self-interrupted[17]. The percentage of patients younger than 50 years in the present study (36.6%) was higher than that 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 rate of self-interruption in the present study. The eradication therapy included mainly lansoprazole as the proton pump inhibitor in the present study's time and location. The reported success rates of lansoprazole for primary eradication therapy are 83.7% to 91.1%[11] and those for secondary eradication therapy are 84.8% to 93.4%[28,29]. Thus, *HP* eradication therapy failed when primary for at least 8.9% of patients and when secondary for at least 6.6% of patients. Similarly, eradication therapy also failed in the present study for patients who had self-interrupted the protocol (the eradication therapy being primary for 238 patients and secondary for 32 patients). However, we believe that the success rate of eradication therapy would be lower because prescribed medications were taken in the appropriate manner by presumably fewer patients who self-interrupted and did not undergo a scheduled UBT than by patients who completed the eradication therapy protocol.

In 2014, the number of *HP* primary eradication packs prescribed to outpatients (in-hospital and external prescriptions) in Japan was 7,168,070[30,31] : 3,966,587 of the Lansap® 400/800 (Takeda Pharmaceutical Co., Ltd., Tokyo, Japan ; containing lansoprazole, 60 mg/day ; amoxicillin, 1,500 mg/day ; and clarithromycin, 400/800 mg/day)[32] and 3,201,483 of the Rabecure® pack 400/800 (Eisai Co., Ltd., Tokyo, Japan ; containing rabeprazole, 20 mg/day ; amoxicillin, 1,500 mg/day ; and clarithromycin, 400/800 mg/day)[33]. Because treatment lasts for 7 days, the estimated number of outpatients who took *HP* primary eradication therapy was 1,024,010 : 566,655 patients received Lansap® 400/800, and 457,355 received Rabecure® pack 400/800. If the self-interruption rate in the present study and the success rates 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 in at least 10,049 patients in Japan. Gastric cancer reportedly develops in 2.9% of patients infected with *HP* during a follow-up period of 7.6 years[34], which would lead to gastric cancer developing in 291 patients during the same period. With *HP* secondary eradication therapy and individually prescribed medications (not pack prescriptions), gastric cancer would develop in more patients. Therefore, from a public health perspective, the incidence of self-interruption and failing to undergo schedule UBTs must be decreased.

A patient age of less than 40 years was associated, in the present study, with poor adherence to the *HP* eradication therapy protocol, which is similar to the results of a recent study in Japan[17]. That study identified younger age (30-49 years) as a factor associated with self-interruption of UBT, although the total number of self-interruption events was low[17]. Likewise, younger age is a common risk factor for poor patient adherence to the treatment of several other diseases[35-37]. The preventive effect of *HP* eradication therapy in reducing the incidence of gastric cancer has been reported to be nearly 100% in patients younger than 40 years[8]. Thus, patients who would receive the greatest benefit from eradication therapy often fail to complete their treatment.

Another finding of the present study was that poor adherence to the *HP* eradication protocol was associated with gastric and duodenal ulcers. Asymptomatic disease is expected to be a major predictor of poor adherence to medication[38]. Similarly, a recovery of symptoms through treatment might result in self-interruption. The present study is the first in Japan to identify the association between poor adherence to eradication therapy and the presence of gastric and duodenal ulcers. To clarify this relationship in greater detail, additional studies are needed. Moreover, we observed good adherence to the treatment protocol in patients who had received a recommendation following a cancer screening result, which might reflect patients' greater awareness of their health.

To prevent self-interruption and to increase adherence during the treatment of other diseases, such as antiretroviral therapy for human immunodeficiency virus infection and direct-acting antivirals for hepatitis C virus infection, various approaches have been proposed[39,40]. For example, for patients infected with human immunodeficiency virus or hepatitis C virus, healthcare professionals are encouraged to explain the significance and expected adverse effects of treatment and to emphasize the importance of adherence. Clinicians are also encouraged to provide treatment with the cooperation of a multidisciplinary healthcare team, including other physicians, nurses, pharmacists, and other

healthcare professionals. Similarly, to increase adherence to *HP* eradication therapy, we should promote patients' understanding of the treatment and provide treatment with the cooperation of a multidisciplinary healthcare team. Another way of increasing adhere might be for local governments or medical institutions to establish follow-up systems, as has been formed in some parts of Japan for the treatment of hepatitis B and C virus infections[41].

Adherence to the *HP* eradication protocol might also involve which medications have been prescribed. In Japan, Vonosap® pack 400/800 and Vonopion® pack (Takeda Pharmaceutical Co., Ltd.), which include the potassium-competitive acid blocker vonoprazan, became available in 2016[18,19]. Because of their high 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 (2 doses), the number of tablets or capsules taken per day (10 or 12), and the treatment duration (7 days) are identical for Lansap®/Rabecure® pack 400/800 and Vonosap® pack 400/800[18,32,33]. Additionally, vonoprazan and lansoprazole, when administered during *HP* primary eradication therapy, reportedly have similar rates of adverse events[16]. Lansap®/Rabecure® pack 400/800 and Vonosap® pack 400/800 also have similar pharmaceutical prices[42]. Considering these factors, which are assumed to affect 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 the present 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.

The present study has several limitations. First, self-interruption was defined as failure to complete a scheduled post-eradication therapy UBT. However, the patients who were believed to have self-interrupted were not followed up and might have undergone 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, self-interruption might have been affected by other factors. A third limitation is that 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, such patients were few and, presumably, had a limited effect on our results. Finally, a fourth limitation of the present study was that it was conducted at a single medical institution, which limits the generalizability of the results. A multicenter study is warranted to ensure greater generalizability.

Conclusion

Approximately 10% of our patients self-interrupted the *HP* eradication protocol. Risk factors for poor adherence to the protocol were an age less than 40 years and the presence of gastric and duodenal ulcers.

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Conflict of Interest Statement

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SYNEOS HEALTH CLINICAL 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.

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