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Association of adjunctive Clostridium butyricum supplementation with eradication outcomes and safety during Helicobacter pylori eradication therapy in adolescents: A multicenter retrospective cohort study

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Abstract

Background

Although probiotics have been found to enhance the efficacy and tolerability of *Helicobacter pylori* (*H. pylori*) eradication therapy, evidence of this effect remains limited in adolescents. We investigated whether *Clostridium butyricum* (Miya-BM) supplementation influenced efficacy and safety in adolescents undergoing first-line *H. pylori* eradication therapy.

Materials and Methods

This retrospective multicenter cohort study included 1169 adolescents diagnosed with *H. pylori* infection through the Saga Prefecture junior high school screening program between 2016 and 2025. Participants received vonoprazan-based triple therapy, and they were grouped by Miya-BM supplementation regimen (0, 4, or 6 tablets/day). The primary outcome was successful first-line eradication as confirmed by urea breath testing. Secondary outcomes included adverse events and second-line eradication outcomes.

Results

The first-line eradication rates were 73.3% (22/30), 85.0% (712/838), and 85.0% (256/301) in the zero-, four-, and six-tablet groups, respectively, reflecting numerically higher eradication rates in patients receiving Miya-BM supplementation. Diarrhea, abdominal pain, and maximum Bristol Stool Scale scores were comparable across the groups. Second-line eradication rates exceeded 94% in all groups.

Conclusions

Supplementation with *C. butyricum* during vonoprazan-based first-line eradication therapy was safe, and it was associated with numerically higher eradication rates without increasing gastrointestinal adverse events in adolescents, although statistical significance was not achieved. Given its excellent safety profile, Miya-BM might represent a useful adjunct to eradication therapy, although confirmatory prospective randomized studies are warranted.

Introduction

Helicobacter pylori (*H. pylori*) remains the most prevalent chronic bacterial infection globally. Although its global prevalence has gradually declined in recent decades, approximately half of the global population is estimated to have been infected, although substantial geographic variation exists.[1, 2] Infection, which is typically acquired during childhood, persists throughout life unless eradicated.[3] Persistent *H. pylori* infection is a well-established cause of chronic gastritis, peptic ulcer disease, gastric mucosa-

associated lymphoid tissue lymphoma, and gastric adenocarcinoma, making it among the most important preventable causes of gastric cancer.[4, 5]

Early *H. pylori* eradication has therefore become an important strategy for gastric cancer prevention.[5] In Japan, several municipalities have implemented population-based screening programs targeting adolescents based on the concept that eradication before the development of advanced gastric mucosal atrophy might provide the greatest long-term benefit.[6]

Despite advances in eradication therapy, treatment success has become increasingly restricted by growing antimicrobial resistance, particularly clarithromycin resistance.[4] Vonoprazan-based triple therapy has achieved higher eradication rates than conventional proton pump inhibitor-based regimens,[7] and it is widely used as the first-line regimen in Japan. Its efficacy and safety have also been evaluated in Japanese adolescents.[8] Nevertheless, eradication failure remains clinically relevant, and gastrointestinal adverse events, including diarrhea and abdominal pain, can negatively affect treatment adherence and quality of life among patients.[9] Consequently, adjunctive interventions that can improve eradication efficacy without increasing adverse events are of considerable clinical interest.

Probiotics have been proposed as promising adjuncts to *H. pylori* eradication therapy. A network meta-analysis of Asian children suggested that probiotic supplementation might improve eradication efficacy and tolerability,[10] consistent with the results of broader meta-analyses of randomized trials.[11] These beneficial effects are believed to be mediated through multiple mechanisms, including modulation of the intestinal microbiota, inhibition of pathogenic bacterial growth, reinforcement of epithelial barrier integrity, and regulation of host immune responses.[11–14] However, because probiotic effects can be strain- and regimen-specific, current pediatric guidelines do not recommend routine adjunctive probiotic therapy for *H. pylori* eradication in children and adolescents.[3]

Clostridium butyricum (Miya-BM®; Miyarisan Pharmaceutical Co., Ltd., Tokyo, Japan) is a butyrate-producing probiotic used in Japan to manage antibiotic-associated gastrointestinal disturbances. Previous clinical studies suggested that concomitant *C. butyricum* administration might reduce eradication therapy-induced alterations in the intestinal microbiota and gastrointestinal adverse events.[12, 13] Butyrate helps maintain intestinal epithelial integrity and regulates intestinal inflammatory responses.[14]

Saga Prefecture has established a population-based *H. pylori* screening program for junior high school students, providing a unique opportunity to evaluate eradication therapy in a large real-world adolescent cohort.[6, 8] Therefore, this study evaluated whether adjunctive Clostridium butyricum supplementation was associated with eradication outcomes, gastrointestinal adverse events, and treatment adherence among adolescents undergoing vonoprazan-based eradication therapy.

Materials & Methods

Study Design and Participants

This retrospective multicenter cohort study included adolescents diagnosed with *H. pylori* infection between April 2016 and March 2025 through the Saga Prefecture junior high school screening program, a population-based gastric cancer prevention initiative.[6] Adolescents with confirmed *H. pylori* infection who received first-line eradication therapy at participating institutions were eligible for inclusion.

Students meeting any of the following criteria were not considered candidates for eradication therapy: known allergy to any of the study drugs; impaired hepatic or renal function; receipt of colchicine; infectious mononucleosis or suspected Epstein–Barr virus infection; and weight < 30 kg. In the present analysis, patients without evaluable first-line eradication outcomes were excluded. Medication adherence was assessed separately from medical records, and it has been presented as a baseline characteristic. The patient selection process is summarized in Fig. 1.

Eradication Therapy

All participants received first-line eradication therapy comprising vonoprazan, amoxicillin, and clarithromycin for 7 days according to the protocol used in the Saga Prefecture screening and eradication program.[8] Successful eradication was confirmed using the ^{13}C-urea breath test, which was performed at least 8 weeks after completion of eradication therapy.[3] Patients who failed first-line therapy subsequently received second-line eradication therapy comprising vonoprazan, amoxicillin, and metronidazole according to routine clinical practice.

Administration of C. butyricum

During eradication therapy, only certain patients received oral *C. butyricum* (Miya-BM) as adjunctive probiotic therapy. According to routine clinical practice, patients were categorized into three groups according to the prescribed daily dose of Miya-BM (0, 4, or 6 tablets/day).

Importantly, Miya-BM administration was determined according to the standardized treatment protocol of each participating institution. In addition, the prescribed dose reflected protocol changes over time within participating institutions rather than individual physician preference or patient characteristics. Consequently, treatment allocation primarily varied according to institutional practices and the treatment period, thereby reducing the likelihood of confounding by indication associated with selective prescription.

Data Collection

Clinical information was extracted retrospectively from electronic medical records. The collected variables included age, sex, prescribed Miya-BM dose, medication adherence, first-line eradication outcome, second-line eradication outcome, adverse events, and stool consistency during treatment.

Medication adherence was defined as completion of the prescribed eradication regimen according to medical records.

Outcomes

The primary outcome was successful first-line *H. pylori* eradication. Secondary outcomes included successful second-line eradication and treatment-related adverse events, including diarrhea, abdominal pain, bloody stool, and the maximum Bristol Stool Scale score recorded during treatment.[15] Diarrhea was evaluated using standardized medical records. A recorded value of zero indicated the absence of diarrhea, whereas any non-zero value indicated diarrhea regardless of frequency or severity. Patients without evaluable diarrhea records were excluded from analyses of this outcome. Abdominal pain, bloody stool, and physician-reported adverse events were analyzed as binary variables according to documentation in the medical records.

Statistical Analysis

Continuous variables were presented as the mean ± SD and compared using one-way analysis of variance. Categorical variables were presented as numbers and percentages and compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Eradication rates were presented with corresponding 95% confidence intervals (CIs). No imputation was performed for missing data, and all analyses were conducted using available-case data.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP Pro version 19 (SAS Institute Inc., Cary, NC, USA).

Ethical Considerations

The study protocol was approved by the Institutional Review Board of Saga University Hospital (approval number: 2015-12-19). Written informed consent for participation in the Saga Prefecture adolescent *H. pylori* screening and eradication program was obtained from all participants and their parents or legal guardians. For this retrospective analysis, the requirement for additional written informed consent was waived by the Institutional Review Board, and an opt-out approach was adopted. The study was additionally conducted following the principles of the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology Statement.

Results

Patient Characteristics

In total, 1169 adolescents who underwent first-line *H. pylori* eradication therapy were included in the analysis. Meanwhile, 30 patients did not receive Miya-BM, 838 patients received 4 tablets/day, and 301 patients received 6 tablets/day.

The baseline characteristics of the cohort are summarized in Table 1. The mean age differed among the three groups (14.90 ± 0.31, 15.03 ± 0.31, and 15.06 ± 0.37 years, respectively; *P* = 0.026), whereas the proportion of male patients was comparable (*P* = 0.337). Medication adherence was high in all groups, but it differed significantly according to Miya-BM supplementation. Completion of all 14 prescribed doses was achieved in 92.0%, 97.8%, and 100% of evaluable patients in the zero-, four-, and six-tablet groups, respectively (*P* = 0.0048).

Table 1
Baseline characteristics of adolescents undergoing first-line *Helicobacter pylori* eradication therapy according to the *Clostridium butyricum* supplementation regimen

Characteristic	**Zero Miya-BM tablets** **(n = 30)**	**Four Miya-BM tablets** **(n = 838)**	**Six Miya-BM tablets** **(n = 301)**	***P***
Age, years, mean ± SD	14.90 ± 0.31	15.03 ± 0.31	15.06 ± 0.37	0.026
Male sex, n (%)	15 (50.0)	454 (54.2)	148 (49.2)	0.337
Medication adherence*				
Completed all 14 doses, n/N (%)	23/25 (92.0)	702/718 (97.8)	249/249 (100)	0.0048
*Medication adherence was assessed only in participants with available adherence records.				
Continuous variables were compared using one-way analysis of variance. Categorical variables were compared using the χ^2 test.				

First-line Eradication Outcomes

The first-line eradication outcomes are presented in Table 2. Successful first-line eradication was achieved in 22/30 patients (73.3%) in the zero-tablet group, 712/838 patients (85.0%) in the four-tablet group, and 256/301 patients (85.0%) in the six-tablet group. Despite the numerically higher eradication rates among patients receiving adjunctive Miya-BM, the overall difference was not statistically significant (*P* = 0.216).

Table 2
First-line *Helicobacter pylori* eradication outcomes according to *Clostridium butyricum* supplementation
A. Eradication outcomes by treatment group

Outcome	Zero Miya-BM tablets (n = 30)	Four Miya-BM tablets (n = 838)	Six Miya-BM tablets (n = 301)	*P*
Successful eradication, n (%)	22 (73.3)	712 (85.0)	256 (85.0)	0.216
Eradication rate, % (95% CI)	73.3 (55.6–85.8)	85.0 (82.4–87.2)	85.0 (80.6–88.6)	0.216

B. Pairwise comparisons of eradication success

Comparison	Relative risk (95% CI)	Odds ratio (95% CI)	Absolute risk difference percentage points (95% CI)	NNT†	*P* ‡
Four tablets vs. zero tablets	1.16 (0.93–1.44)	2.05 (0.90–4.72)	11.6 (−1.1 to 29.6)	9	0.116
Six tablets vs. zero tablets	1.16 (0.93–1.45)	2.07 (0.87–4.93)	11.7 (−1.5 to 29.9)	9	0.115
Six tablets vs. four tablets	1.00 (0.95–1.06)	1.01 (0.70–1.46)	0.1 (−4.9 to 4.5)	—	>0.999

Confidence intervals (CIs) for individual eradication rates were calculated using the Wilson method. The overall comparison among the three groups was performed using the Pearson χ^2 test.

†NNT, number needed to treat. NNT was calculated as the reciprocal of the absolute risk difference and rounded up to the nearest whole number. NNT should be interpreted cautiously because the corresponding 95% CIs for the risk differences included zero. NNT was not reported for the comparison between the six- and four-tablet groups because the absolute difference was clinically negligible.

‡Pairwise *P* values were calculated using the two-sided Fisher exact test without adjustment for multiple comparisons. After Holm adjustment, the adjusted *P* values were 0.344, 0.344, and 1.000, respectively.

Pairwise comparisons similarly revealed no statistically significant differences among the treatment groups. No significant dose–response relationship was observed in the Cochran–Armitage trend test (*P* = 0.255).

Treatment-related Adverse Events

Treatment-related adverse events are summarized in Table 3. Among patients with evaluable questionnaire data, diarrhea occurred in 37.5%, 36.2%, and 33.2% of patients in the zero-, four-, and six-tablet groups, respectively (*P* = 0.74). Similarly, the frequencies of abdominal pain (25.0%, 27.7%, and

25.2%, respectively; *P* = 0.72) and the mean maximum Bristol Stool Scale score (5.38 ± 1.03, 5.21 ± 1.14, and 5.12 ± 1.09, respectively; *P* = 0.49) did not differ significantly among the groups. No patients reported bloody stool during treatment. Overall, adjunctive Miya-BM supplementation was well tolerated, and it was not associated with an increase in patient-reported gastrointestinal adverse events.

Table 3
Gastrointestinal adverse events during first-line *Helicobacter pylori* eradication therapy according to *Clostridium butyricum* supplementation

Outcome	Zero Miya-BM tablets	Four Miya-BM tablets	Six Miya-BM tablets	*P*
Patients evaluable for adverse events, n	24	556	247	—
Diarrhea, n/N (%)	9/24 (37.5)	201/556 (36.2)	82/247 (33.2)	0.74
Abdominal pain, n/N (%)	6/24 (25.0)	154/555 (27.7)	62/246 (25.2)	0.72
Bloody stool, n/N (%)	0/24 (0.0)	0/556 (0.0)	0/246 (0.0)	—
Maximum Bristol Stool Scale score, mean ± SD	5.38 ± 1.03	5.21 ± 1.14	5.12 ± 1.09	0.49†
Patients with missing questionnaire data were excluded from the analysis for each patient-reported outcome.				
Diarrhea was defined as one or more diarrheal episodes during first-line eradication therapy.				
Abdominal pain and bloody stool were analyzed as patient-reported binary outcomes (“present” or “absent”).				
†One-way analysis of variance for comparisons of maximum Bristol Stool Scale scores.				

Second-line Eradication Outcomes

Second-line eradication outcomes are presented in Table 4. Among patients who underwent second-line eradication therapy, successful eradication was achieved in all eight patients (100%) in the zero-tablet group, 117/124 patients (94.4%) in the four-tablet group, and 44/45 patients (97.8%) in the six-tablet group, with no significant differences among the groups (*P* = 0.58). These findings indicate that adjunctive Miya-BM supplementation had no measurable influence on the efficacy of second-line eradication therapy.

Table 4
Second-line *Helicobacter pylori* eradication outcomes according to *Clostridium butyricum* supplementation

Outcome	Zero Miya-BM tablets (n = 8)	Four Miya-BM tablets (n = 124)	Six Miya-BM tablets (n = 45)	*P*
Successful eradication, n (%)	8 (100.0)	117 (94.4)	44 (97.8)	0.58*
Eradication rate, % (95% CI)	100.0 (67.6–100.0)	94.4 (88.9–97.3)	97.8 (88.4–99.9)	0.58*
Confidence intervals (CIs) were calculated using the Wilson score method.				
*Overall comparison was performed using Fisher's exact test because of the small sample size and low expected cell counts.				

Discussion

The present multicenter retrospective cohort study evaluated the efficacy and safety of adjunctive *C. butyricum* during vonoprazan-based *H. pylori* eradication therapy in 1169 adolescents identified through a population-based screening program. Although Miya-BM supplementation was not associated with a significant improvement in first-line eradication rates, patients receiving Miya-BM exhibited numerically higher eradication rates than those who did not receive supplementation. In addition, Miya-BM was well tolerated, with no increase in gastrointestinal adverse events, and medication adherence was significantly higher among patients receiving Miya-BM. These findings suggest that adjunctive *C. butyricum* supplementation may represent a practical adjunct to routine eradication therapy in adolescents.

Several meta-analyses have suggested that probiotic supplementation modestly improves *H. pylori* eradication success while reducing antibiotic-associated adverse events.[10, 11] The proposed mechanisms include modulation of the intestinal microbiota, inhibition of pathogenic bacterial growth, reinforcement of epithelial barrier function, and immunomodulatory effects.[11–14] However, considerable heterogeneity exists among probiotic strains, treatment regimens, and study populations, and current pediatric guidelines do not recommend routine use of a specific probiotic because of insufficient high-quality evidence.[3] Our findings align with this body of evidence. Although statistical significance was not achieved, eradication rates were approximately 12 percentage points higher in both Miya-BM groups than in the group without probiotic supplementation, suggesting a potential clinical benefit that warrants further investigation in adequately powered prospective studies.

An important finding of the present study was the high level of treatment adherence observed among patients receiving Miya-BM. Because successful *H. pylori* eradication depends heavily on the completion of combination antibiotic therapy, improved adherence might contribute to favorable treatment

outcomes.[3, 11] Although the mechanism underlying this association cannot be determined in the present observational study, preservation of intestinal homeostasis through butyrate production and mitigation of antibiotic-associated gastrointestinal discomfort might have facilitated treatment completion.[12–14] From a clinical perspective, treatment adherence could have similar importance as direct antimicrobial effects when considering adjunctive probiotic therapy.

Concerning safety, patient-reported gastrointestinal symptoms, including diarrhea, abdominal pain, bloody stool, and stool consistency, were comparable among the groups. Although diarrhea occurred less frequently in patients receiving Miya-BM, the difference did not reach significance. Differences in institutional reporting practices or residual confounding might have influenced these results, and a causal relationship could not be established. Previous studies reported that concomitant *C. butyricum* can attenuate eradication therapy-induced disruption of the intestinal microbiota and reduce gastrointestinal adverse events.[12, 13] Nevertheless, the lack of an increase in patient-reported gastrointestinal symptoms supports the overall safety of adjunctive Miya-BM administration during eradication therapy.

One of the major strengths of this study was its unique study design. Unlike many retrospective observational studies in which probiotic administration was determined by individual physician discretion or patient condition, Miya-BM supplementation was primarily determined according to standardized institutional treatment protocols and protocol changes over time in the present study. Consequently, treatment allocation depended largely on institutional practice and treatment period rather than patient-specific clinical characteristics, thereby reducing the likelihood of confounding by indication. Furthermore, this study included more than 1100 adolescents from a population-based screening program,[6, 8] providing the largest real-world cohort-based evaluation of adjunctive *C. butyricum* during adolescent *H. pylori* eradication therapy. To our knowledge, this represents one of the largest real-world cohort studies evaluating adjunctive Clostridium butyricum during adolescent H. pylori eradication therapy. The high treatment adherence and standardized follow-up using the ^{13}C-urea breath test further strengthen the reliability of the findings.

Several limitations should also be acknowledged. First, this was a retrospective observational study, and residual confounding could not be excluded despite the institutional protocol-based allocation of Miya-BM. Second, few patients did not receive Miya-BM, limiting statistical power and resulting in wide CIs. Third, gastrointestinal symptoms were evaluated using routine clinical questionnaires rather than validated symptom severity scales, and missing questionnaire data reduced the number of evaluable patients for some analyses. Finally, this study was conducted within a single prefectural screening program in Japan, and the findings might not be directly generalizable to adult populations or healthcare systems with different eradication strategies.

Conclusion

An adjunctive Miya-BM supplementation during vonoprazan-based *H. pylori* eradication therapy in adolescents achieved high safety and excellent medication adherence. Although no significant improvement in eradication rates was observed, the numerically higher eradication rates and favorable safety profiles suggest that Miya-BM might provide clinically meaningful supportive benefits during eradication therapy. Multicenter randomized controlled trials are warranted to clarify the efficacy of *C. butyricum* supplementation and identify patient populations most likely to benefit.

List for abbreviations

H. pylori = *Helicobacter pylori*, *Clostridium butyricum* = Miya-BM, confidence intervals = Cis

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Saga University Hospital (approval number: 2015-12-19). The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030632). Written informed consent for participation in the Saga Prefecture adolescent *Helicobacter pylori*screening and eradication program was obtained from all participants and their parents or legal guardians. For the present retrospective analysis, the requirement for additional written informed consent was waived by the Institutional Review Board, and an opt-out approach was adopted.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: TK and KF.

Data curation: YH.

Formal analysis: KF.

Investigation: TK, HE, TN, II, NT, SI, KH, KF, MY, TeK, KY, TY, HK, SF, MS, KM, EM, AW and KF.

Methodology: KF and ME.

Supervision: ME.

Writing – original draft: TK.

Writing – review & editing: All authors read and approved the final manuscript.

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Clinical trial number: Not applicable.

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Figures

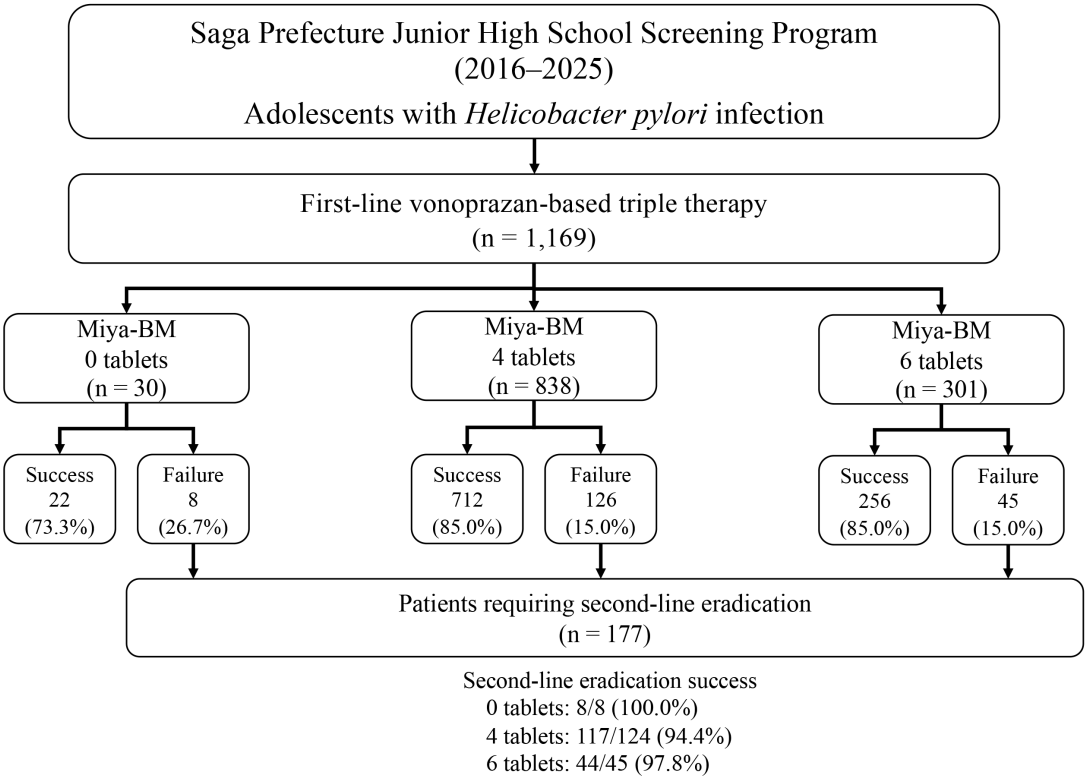


Figure 1

Patient flow and eradication outcomes according to adjunctive *Clostridium butyricum* (Miya-BM) supplementation.

Adolescents diagnosed with *Helicobacter pylori* infection through the Saga Prefecture junior high school screening program (2016–2025) received first-line vonoprazan-based triple therapy, and they were categorized according to the prescribed daily dose of adjunctive Miya-BM (zero, four, or six tablets per day). The numbers of patients with successful and unsuccessful first-line eradication are presented for each group. Patients who failed first-line therapy subsequently underwent second-line eradication therapy, and second-line eradication outcomes are summarized.