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CLINICAL TRIAL REPORT

Vonoprazan–Amoxicillin Dual Therapy with or Without *Saccharomyces boulardii* Supplementation as a Rescue Regimen for *Helicobacter pylori* Infection

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Background: Whether the incorporation of *Saccharomyces boulardii (S. boulardii)* into vonoprazan–amoxicillin dual therapy contributes to improved eradication rate and a lower frequency of adverse events in rescue regimens for *Helicobacter pylori* (*H. pylori*) infection has yet to be established.

Methods: In a single-center, randomized controlled trial, 190 adults with previous *H. pylori* treatment failure were assigned to receive either vonoprazan (20 mg twice daily) plus amoxicillin (750 mg three times daily) (VA group) or the same regimen with S. boulardii (250 mg twice daily) (VAS group) for 14 days. Eradication rates, compliance, adverse events, and safety were assessed. Risk factors influencing the eradication rate were explored.

Results: Based on intention-to-treat analysis, *H. pylori* eradication rates were 80.0% in the VA group and 92.6% in the VAS group (P = 0.011), and per-protocol analysis yielded eradication rates of 85.4% and 94.6%, respectively (P = 0.037). There were no significant differences in eradication rates for either the VA regimen (P = 0.736) or the VAS regimen (P = 0.431) based on the number of previous treatment failures. However, a history of prior furazolidone use reduced the eradication rate of VAS therapy. The incidence of adverse events was significantly lower in the VAS group (11.6%) than it was in the VA group (32.6%; P < 0.001). Both groups showed similar good compliance and safety.

Conclusion: Supplementing vonoprazan–amoxicillin dual therapy with *S. boulardii* significantly increases *H. pylori* eradication rates and reduces adverse events, offering an effective and simple rescue treatment unaffected by previous treatment failures.

Trial Registration: Chinese Clinical Trial Registry No. ChiCTR2300075382, September 4, 2023.

Keywords: *Helicobacter pylori*, vonoprazan, amoxicillin, rescue treatment, *Saccharomyces boulardii*

Introduction

Helicobacter pylori (*H. pylori*) infection is considered a serious health issue worldwide. It is not only closely associated with digestive system disorders such as chronic gastritis, peptic ulcers, and gastric cancer,[1] but also increases the risk of developing cardiovascular and hematological diseases.[2] *H. pylori* is classified as a class I biocarcinogen.[3] Approximately 50% of the population of China is estimated to be infected with *H. pylori*.[4] To prevent the occurrence and development of the aforementioned diseases, it is necessary to carry out effective *H. pylori* eradication programs.

According to the Maastricht VI/Florence Consensus Report, a 14-day bismuth-containing quadruple therapy (BQT) is recommended as the primary treatment option in regions where clarithromycin resistance is prevalent.[5] However, the growing use of antibiotics in recent years—alongside issues such as poor patient compliance, irregular dosing, and an increase in drug-related side effects—is associated with a gradual reduction in the eradication rate of the BQT regimen.[6,7]

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Repeated failure of *H. pylori* eradication imposes a significant clinical and economic burden, also leading to increased patient anxiety.[8] Hence, it is urgent to explore alternatives to *H. pylori* treatment.

Compared to PPIs, vonoprazan—a novel potassium-competitive acid blocker (P-CAB)—demonstrates a more potent and sustained suppression of gastric acid secretion. Therefore, it can be used in dual-therapy regimens. A retrospective analysis carried out in China demonstrated an *H. pylori* eradication rate of 92.5% using a dual rescue therapy comprising vonoprazan–amoxicillin (VA).[9] However, heterogeneity in treatment protocols was noted, with variations in the frequencies of vonoprazan and amoxicillin doses. Qiu et al conducted a prospective randomized controlled trial (RCT) and reported an eradication rate of 97.8% with the rescue therapy comprising vonoprazan 20 mg twice daily + amoxicillin 750 mg four times daily.[10] However, taking amoxicillin four times daily may increase patient inconvenience and reduce compliance. Therefore, it is necessary to further optimize the dose and frequency of amoxicillin for use in a rescue treatment.

Probiotic supplementation has also been proposed as an alternative rescue approach for *H. pylori* infection.[11] Among various probiotics, *Saccharomyces boulardii (S. boulardii)* has garnered particular attention due to its unique characteristics, including resistance to gastric acid and stability during antibiotic co-administration.[12,13] A meta-analysis has shown that supplementing the standard triple therapy with *S. boulardii* increases the eradication rates of *H. pylori* and decreases the overall incidence of adverse effects.[14] In our previous pilot study with a relatively small sample size, we found that VA dual therapy combined with *S. boulardii* (VAS) demonstrated good safety and achieved a high eradication rate of 92.60%.[15] However, due to the lack of a control group in the single-arm design, direct comparisons of the safety and efficacy between the VA-dual and VAS regimens could not be performed.

Accordingly, the safety and efficacy of the VA-dual and VAS regimens as rescue therapies for *H. pylori* infection are being evaluated and compared in this prospective study.

Materials and Methods

Study Design

This investigation was designed as a prospective, randomized controlled trial conducted at a single center. The trial was implemented at the Third Affiliated Hospital of Nanjing Medical University in Changzhou, China, spanning from February 2024 to October 2024. The study protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2300075382) on September 4, 2023.

Eligible patients were enrolled consecutively in accordance with predefined inclusion criteria. Upon recruitment, demographic and clinical characteristics were systematically recorded for each participant. During follow-up, researchers also documented adverse events and medication status, as well as assessed the symptoms of the patients at baseline, end of treatment, and 4 weeks post-treatment. To assess therapeutic efficacy, all participants were instructed to undergo[13] C-urea breath test (13C-UBT) within 4–6 weeks following the eradication regimen.

Study Participants

Patients over 18 years of age, who presented to the Department of Gastroenterology at the Third Affiliated Hospital of Nanjing Medical University, had experienced at least one unsuccessful *H. pylori* eradication therapy, and had not received any treatment for a minimum of six months following the last intervention were included. The inclusion criteria were as follows: (1) age over 18 years, irrespective of gender; (2) at least one previous failure of *H. pylori* eradication treatment; and (3) a treatment-free interval of at least six months after the last eradication attempt. The exclusion criteria were: (1) continuous use of PPIs, P-CABs, or H2-receptor antagonists within two weeks before treatment, or administration of antibiotics or bismuth compounds within one month before starting the treatment; (2) known allergy or contraindication to any medication included in the study protocol; (3) pregnancy or lactation; (4) presence of severe concomitant diseases such as cardiac, hepatic, or renal dysfunction; (5) history of gastric surgery; and (6) absence of informed consent.

Grouping and Medication

At the research center, eligible patients were randomly assigned in a 1:1 ratio to one of two treatment groups via a computer-generated random sequence to receive a 14-day intervention. Allocation was concealed with opaque sealed envelopes. All

participants and researchers were aware of their assigned treatment regimen after randomization. The dosages and administration frequencies were selected based on our previous pilot study, which demonstrated good safety and a high eradication rate with the VAS regimen.[15] The specific medication protocols for the two treatment groups are outlined below:

1. VA–dual group (VA): Patients in this group were prescribed vonoprazan at a dose of 20 mg twice daily, in conjunction with amoxicillin at 750 mg three times daily. The medications were sourced from Takeda Pharmaceutical (Tokyo, Japan) and Federal Pharmaceutical (Hong Kong, China), respectively.
2. VA–dual plus *S. boulardii* (VAS) group: Patients in this group received the same dual therapy as that received by the VA group, with the addition of *S. boulardii* sachets at a dose of 250 mg twice daily, manufactured by Laboratoires BIOCODEX (France).

The dosing schedule required vonoprazan and *S. boulardii* to be taken prior to meals, while amoxicillin was administered following food intake.

Diagnosis of H. Pylori Infection

H. pylori infection was detected by performing 13C-UBT. All patients underwent a repeat 13C-UBT 4–6 weeks after the completion of eradication therapy to assess *H. pylori* status. Infection was considered positive when the δ value exceeded or equaled the baseline value of 4 and negative when it was below the baseline value of 4.

Safety and Compliance

Patients were informed about potential adverse events before taking the medication. They were required to document these events on a predesigned case report form. The severity of adverse events was categorized into three levels:

1. Mild: causing discomfort without affecting daily life;
2. Moderate: leading to discomfort and interfering with daily life; and
3. Severe: causing discomfort necessitating discontinuation of the treatment.

To determine the frequency of adverse events, the number of patients who experienced each event was recorded. Multiple adverse events that occurred in one patient were counted separately. The trial investigator was available for contact throughout the treatment period to address any adverse events. Compliance was assessed based on pill count. Good compliance was defined as taking ≥90% of the study medication.[16] Patients exhibiting poor compliance were excluded from PP analysis.

Outcomes

The primary outcome was the eradication rate of *H. pylori*. The secondary outcomes included the incidence of adverse events, safety, patient compliance, and the factors potentially influencing *H. pylori* eradication.

Calculation of Sample Size and Statistical Analysis

This study adopted an RCT design. The experimental group was the VAS group, and the control group was the VA group. The eradication rate of *H. pylori* in the study subjects was the main observed evaluation index. Based on eradication rates reported in previous studies, the VA group was expected to achieve an eradication rate of 76.2%[17] and the VAS group 92.3%.[15] Using PASS 2021, with an 80% power (1 - β) and a two-sided α level of 0.05, the minimum required sample size was determined to be 80 cases per group. To account for an estimated dropout rate of 15%, the target enrollment was increased to 95 participants per group, totaling 190 participants.

IBM SPSS Statistics, version 29.0 (SPSS Inc., Chicago, IL, USA) was used for statistical data analysis. A two-sided $P < 0.05$ was considered statistically significant. Categorical variables were described as percentages or frequencies. Continuous variables with a normal distribution were described as mean ± standard deviation. For categorical variables, intergroup differences were evaluated using Pearson's chi-square or Fisher's exact test. For continuous variables, Student's *t*-test was used.

To identify potential predictors of eradication success, we performed subgroup analyses within each treatment group for demographic and clinical factors (sex, age, BMI, lifestyle factors, gastroscopy findings, number of previous treatment failures, and prior antibiotic use). These analyses aimed to explore whether any of these factors influenced the *H. pylori* eradication rate with the VA or VAS regimen.

Missing data were handled as follows: in the ITT analysis, patients with missing 13C-UBT results were considered treatment failures, and in the PP analysis, only patients with complete data and good compliance were included. For liver and kidney function tests, only patients with complete pre- and post-treatment data were included in the analysis.

Results

Patient Enrollment and Baseline Characteristics

The study design is illustrated in Figure 1. Using a computer-generated randomization table, patients were allocated to either the intervention or control group. Between February 2024 and October 2024, a total of 203 patients underwent eligibility screening. Of these, 13 were excluded: 1 was under the age of 18, 4 had received eradication therapy within the previous 6 months, 2 were allergic to amoxicillin, 2 had severe hepatic dysfunction, and 4 declined to participate. The remaining 190 patients were subsequently randomized to receive either the 14-day VA or VAS regimen as part of *H. pylori* rescue therapy.

Baseline demographic and clinical characteristics are presented in Table 1. There were no statistically significant differences between the two groups in terms of sex, age, body mass index (BMI), concomitant disease (hypertension or diabetes mellitus), lifestyle factors (cigarette smoking or drinking), or gastroscopic results (all $P > 0.05$). The average age of the patients in the VA group (men = 47.37%) was 49.04, while it was 48.58 in the VAS group (men = 34.74%).

Eradication Rate and Factors Influencing Efficacy

The primary outcome variable was the eradication rates in each group using ITT and PP analysis (Table 2). The eradication rates of VA versus VAS group were 80.0% (76/95; 95% CI: 70.8%–86.9%) versus 92.6% (88/95; 95% CI: 85.7%–96.4%) in the ITT analysis, and 85.4% (76/89; 95% CI: 76.5%–91.4%) versus 94.6% (88/93; 95% CI: 88.2%–97.7%) in the PP

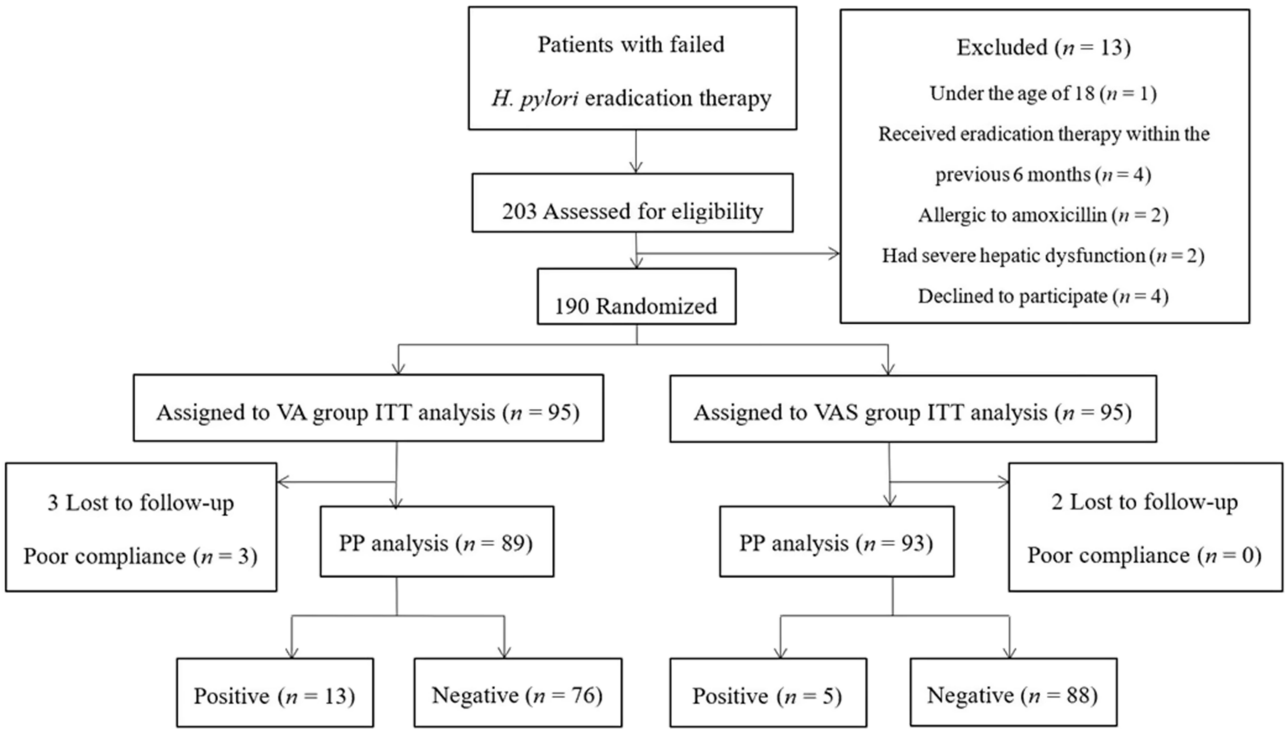

Figure 1 Design of two therapeutic regimens and flowchart of the study.

Table 1 Baseline Demographics and Clinical Characteristics of Study Subjects

Variables	Total (n = 190)	VA group (n = 95)	VAS group (n = 95)	Statistic	*P*-value
Sex, n (%)				$\chi^2 = 3.132$	0.077
Women	112 (58.95)	50 (52.63)	62 (65.26)		
Men	78 (41.05)	45 (47.37)	33 (34.74)		
Age (years)	48.81 ± 11.77	49.04 ± 12.64	48.58 ± 10.91	$t = 0.270$	0.787
Body mass index (kg/m^2)	22.98 ± 2.78	23.16 ± 2.86	22.80 ± 2.70	$t = 0.885$	0.377
Concomitant disease					
Hypertension, n (%)	43 (22.63)	26 (27.37)	17 (17.89)	$\chi^2 = 2.435$	0.119
Diabetes mellitus, n (%)	15 (7.89)	5 (5.26)	10 (10.53)	$\chi^2 = 1.810$	0.179
Lifestyle factors					
Cigarette Smoking, n (%)	13 (6.84)	7 (7.37)	6 (6.32)	$\chi^2 = 0.083$	0.774
Drinking, n (%)	11 (5.79)	6 (6.32)	5 (5.26)	$\chi^2 = 0.096$	0.756
Gastroscopy findings, n (%)					
Atrophic gastritis	86 (45.26)	41 (43.16)	45 (47.37)	$\chi^2 = 0.340$	0.560
Non-atrophic gastritis	41 (21.58)	17 (17.89)	24 (25.26)	$\chi^2 = 1.524$	0.217
Peptic ulcer	12 (6.32)	6 (6.32)	6 (6.32)	$\chi^2 = 0.000$	1.000
No gastroscopy done	51 (26.84)	31 (32.63)	20 (21.05)	$\chi^2 = 3.243$	0.072

Abbreviations: VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and *S. boulardii* for 14 days.

Table 2 Comparison of the *Helicobacter Pylori* Eradication Rates in Two Groups

Analysis	VA group	VAS group	Difference in Eradication Rate (%)	*P*-value	χ^2
PP	76/89 (85.4)	88/93 (94.6)	9.2	0.037	4.38
95% CI	76.5–91.4	88.2–97.7	1.0–18.6		
ITT	76/95 (80.0)	88/95 (92.6)	12.6	0.011	6.45
95% CI	70.8–86.9	85.7–96.4	3.2-22.1		

Abbreviations: VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and S. boulardii for 14 days; CI, Confidence interval; PP, Per-protocol; ITT, Intention-to-treat.

analysis. In the test of VAS compared with VA therapy, the difference in eradication rates between the two groups was 12.6% (95% CI: 3.2%–22.1%) in the ITT analysis and 9.2% (95% CI: 1.0%–18.6%) in the PP analysis. A significant difference in eradication rates was observed between the VAS and VA groups in both analyses, favoring the VAS regimen (both $P < 0.05$; Table 2).

Factors potentially influencing *H. pylori* eradication in ITT analysis are shown in Tables 3 and 4. The use of clarithromycin, levofloxacin, nitroimidazoles, and amoxicillin had no impact on the eradication rate achieved using

Table 3 Previous Antibiotic Use Influencing *Helicobacter Pylori* Eradication in ITT Analysis

Antibiotic History	VA Group		VAS Group	
	Eradication Rate % (n/N)	*P*-value	Eradication Rate % (n/N)	*P*-value
Clarithromycin				
Yes	79.3 (46/58)	1.000	93.8 (61/65)	0.058
No	100 (2/2)		72.7 (8/11)	
Levofloxacin				
Yes	81.0 (17/21)	1.000	90.0 (36/40)	1.000
No	79.5 (31/39)		91.7 (33/36)	
Nitromidazoles				
Yes	88.0 (22/25)	0.190	92.9 (26/28)	1.000
No	74.3 (26/35)		89.6 (43/48)	

(*Continued*)

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Table 3 (Continued).

Antibiotic History	VA Group		VAS Group	
	Eradication Rate % (n/N)	*P*-value	Eradication Rate % (n/N)	*P*-value
Amoxicillin				
Yes	63.6 (7/11)	0.206	86.4 (19/22)	0.406
No	83.7 (41/49)		92.6 (50/54)	
Furazolidone				
Yes	100.0 (2/2)	1.000	40.0 (2/5)	0.005
No	79.3 (46/58)		94.4 (67/71)	
Doxycycline				
Yes	75.0 (3/4)	1.000	0	-
No	80.4 (45/56)		0	

Abbreviations: ITT, Intention-to-treat; VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and *S. boulardii* for 14 days.

Table 4 Demographic and Clinical Factors influencing *Helicobacter Pylori* Eradication in ITT Analysis

Influencing Factor	VA Group		VAS Group	
	Eradication Rate % (n/N)	*P*-value	Eradication Rate % (n/N)	*P*-value
Sex				
Men	84.4 (38/45)	0.304	90.3 (28/31)	0.713
Women	76.0 (38/50)		92.2 (59/64)	
Age (years)				
<50	77.8 (35/45)	0.607	93.8 (45/48)	0.486
≥50	82.0 (41/50)		89.4 (42/47)	
Body mass index				
<24	77.6 (45/58)	0.461	93.8 (60/64)	0.431
≥24	83.8 (31/37)	0.206	87.1 (27/31)	1.000
Hypertension	88.5 (23/26)	1.000	94.1 (16/17)	1.000
Yes	76.8 (53/69)		91.0 (71/78)	
No	80.0 (4/5)		90 (9/10)	
Diabetes mellitus	80.0 (72/90)		91.8 (78/85)	
Yes				
No				
Cigarette smoking				
Yes	85.7 (6/7)	1.000	85.7 (6/7)	0.471
No	79.5 (70/88)		92.0 (81/88)	
Drinking				
Yes	83.3 (5/6)	1.000	83.3 (5/6)	0.419
No	79.8 (71/89)		92.1 (82/89)	
Gastroscopy findings	70.7 (29/41)	1.000	95.6 (43/45)	0.071
Atrophic gastritis	70.6 (12/17)		79.2 (19/24)	
Non-atrophic gastritis	83.3 (5/6)		83.3 (5/6)	
Peptic ulcer				
Eradication failure times				
One	79.1 (53/67)	0.736	93.8 (60/64)	0.431
Two or more	82.1 (23/28)		87.1 (27/31)	

Abbreviations: ITT, Intention-to-treat; VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and *S. boulardii* for 14 days.

either VA or VAS therapy. However, the eradication rate was found to be significantly lower in patients with a prior history of furazolidone use (n = 5) compared to those without such a history (40.0% [2/5] vs. 94.4% [67/71]; $P = 0.005$) in the VAS group (Table 3). Moreover, the eradication rates obtained using VA ($P = 0.736$) and VAS ($P = 0.431$) therapies did not show any significant differences based on the number of prior treatment failures. Other factors such as gender, age, BMI, smoking, alcohol consumption, and gastroscopy results were analyzed and were not found to be risk factors for eradication failure (Table 4).

Adverse Events and Patient Compliance

Table 5 presents the adverse events reported by all patients. The incidence of adverse events was significantly lower in the VAS group (11.6%, 11/95 patients) than it was in the VA group (32.6%, 31/95 patients; $P < 0.001$). In the VA group, the majority of adverse events were mild and resolved spontaneously, except for two patients who developed rashes, refused to continue the rescue treatment, and ultimately recovered after an anti-allergy therapy. Another patient ceased treatment because of moderate bloating, which resolved spontaneously. Three patients were lost to follow-up in the VA group. None of the patients in the VAS group discontinued the medication due to adverse events; however, two patients were lost to follow-up.

There were no significant differences in adherence between the VA and VAS groups (93.7% vs. 97.9%, $P = 0.279$) (Table 5). Serum chemistry tests, available for 60 patients in the VA group and 51 in the VAS group, showed no significant differences in liver and kidney functions before and after treatment (Table 6).

Table 5 Adverse Events

Variables, n/N (%)	VA	VAS	*P*
Total	31/95 (32.6%)	11/95 (11.6%)	<0.001
Constipation	3	0	
Abdominal pain	3	2	
Diarrhea	3	1	
Abdominal distension	5	2	
Abdominal discomfort	4	1	
Dry mouth	2	1	
Bitter taste	1	0	
Nausea	4	1	
Vomiting	2	0	
Sleepiness	1	0	
Rash	2	3	
Itchy skin	1	0	
Discontinued due to AEs	3/95 (3.2%)	0/95 (0%)	0.246
Lost in follow-up	3/95 (3.2%)	2/95 (2.1%)	1.000
Adherence, n/N (%)	89/95 (93.7%)	93/95 (97.9%)	0.279

Abbreviations: AE, adverse event; VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and *S. boulardii* for 14 days.

Table 6 Comparison of Liver and Kidney Function Before and After the Treatment

Variables		Before	After	Statistics	P-value
Total bilirubin	VA (n = 60)	13.80(10.78,15.90)	12.90(10.30,17.35)	$Z = -0.070$	0.944
[μmol/L $\bar{x} \pm s$, M(Q_1,Q_2)]	VAS (n = 51)	14.16±4.00	15.30±5.07	$t = -1.804$	0.077
ALT	VA (n = 60)	20.36±7.61	19.71±8.59	$t = 0.869$	0.388
[U/L, $\bar{x} \pm s$, M(Q_1,Q_2)]	VAS (n = 51)	16.40(12.50,24.60)	17.50(12.20,25.30)	$Z = -1.497$	0.134
Creatinine	VA (n = 60)	63.93±12.02	65.35±13.40	$t = -1.378$	0.171
(μmol/L, $\bar{x} \pm s$)	VAS (n = 51)	61.68±12.75	62.85±12.67	$t = -1.637$	0.108

Abbreviations: VA, treatment with vonoprazan and amoxicillin for 14 days; VAS, treatment with vonoprazan, amoxicillin, and *S. boulardii* for 14 days; ALT, alanine aminotransferase.

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Discussion

To the best of our knowledge, this is the first study to compare the efficacy and safety of the VA dual therapy with the VAS therapy as a rescue treatment for patients with *H. pylori*. The VAS regimen afforded consistently high eradication rates above 90% in both analyses, superior to those below this threshold obtained with the VA regimen. In addition, the incidence of adverse events was significantly lower in the VAS group (11.6%) than it was in the VA group (32.6%). These findings indicate that the addition of *S. boulardii* to the VA dual therapy may substantially improve eradication efficacy while concurrently decreasing the incidence of adverse events.

Some studies have shown that vonoprazan combined with 3000 mg of amoxicillin daily is a satisfactory rescue treatment for *H. pylori*.[9,10,18] However, this high-dose amoxicillin VA dual therapy has diarrhea and abdominal pain as the common adverse events, which were likely related to the high-dose use of amoxicillin. Existing evidence indicates that a daily amoxicillin dose of 2 g is suboptimal, whereas a total daily dose of 3 g or 2.25–3.00 g, administered in divided doses every 6 to 8 hours, may provide improved therapeutic outcomes.[19] To reduce the incidence of adverse events associated with high doses of amoxicillin, we set the dosage of amoxicillin at 750 mg three times daily. Multiple studies have indicated that a prolonged antibiotic treatment may result in the selection of drug-resistant bacteria and can cause serious adverse effects such as severe diarrhea.[20,21] Recent studies have also revealed that the eradication of *H. pylori* may result in the dysbiosis of the gastrointestinal microbiota; however, probiotic supplementation has the potential to restore the disturbed microbiota in some patients.[22] Therefore, we added *S. boulardii* to the VA dual regimen.

The underlying mechanisms by which the VAS regimen contributes to *H. pylori* eradication may include the following:

(1) Vonoprazan, a potent P-CAB, is capable of inducing a faster and more sustained suppression of gastric acid than that typically achieved with PPIs.[23] Thus, the use of vonoprazan for *H. pylori* eradication facilitates rapid establishment and prolonged maintenance of optimal pH conditions in the stomach. Moreover, because vonoprazan metabolism predominantly occurs via cytochrome P450 (CYP) 3A4 and is unaffected by CYP2C19 genetic polymorphisms, it ensures a stable acid-suppressive effect with limited interindividual variation.[24]

(2) *S. boulardii* exhibits neuraminidase activity that is selective to α-(2,3)-linked sialic acid, a known ligand for *H. pylori* adhesins, thereby interfering with bacterial attachment to the duodenal mucosa.[25] Additionally, *S. boulardii* has been shown to elevate the concentrations of short-chain fatty acids and other antimicrobial substances, contributing to the inhibition of *H. pylori* growth and proliferation.[26] It may also upregulate the secretion of immunoglobulins, including secretory IgA, thereby enhancing mucosal immune defense.[27]

Our results showed that the VAS regimen afforded a satisfactory eradication rate, independent of the number of prior failed treatments ($P = 0.431$). There was no difference in the eradication rates between patients with prior amoxicillin use and those without (86.4% vs 92.6%, $P = 0.406$). However, prior furazolidone use was associated with a lower eradication rate with the VAS regimen ($P = 0.005$). Furazolidone is typically employed as a rescue therapy for *H. pylori* infections and is considered a last-resort option. This is a preliminary finding that requires validation in a larger sample. Therefore, for patients with prior furazolidone treatment failure, we recommend performing individualized bacterial drug resistance analysis to accurately identify sensitive antibiotics for the subsequent rescue therapy.

While the eradication rate is the primary indicator for evaluating treatment plans, other factors such as adverse events and compliance are also important. Our findings demonstrated that the VAS regimen, compared to the VA regimen, reduced the incidence of total adverse events. Notably, the low incidence of diarrhea in both the VA and VAS groups may be due to the low dose of amoxicillin used in our trial. In addition, the before-and-after comparisons of liver and kidney function indicators showed that the regimen was safe. Both treatment groups showed very good patient compliance, which can be attributed to multiple factors, including a simple eradication regimen, strong treatment motivation of the patients, close follow-up communication during medication, and timely reminders after medication.

This study has some limitations. First, the research was conducted at a single center with a relatively limited sample size, coupled with small subgroup samples, which may restrict the broader applicability of the findings. Therefore, large-scale, high-quality, and multicenter RCTs should be carried out to confirm our results. Second, antimicrobial susceptibility testing for *H. pylori* was not undertaken, precluding the assessment of whether resistance to amoxicillin influenced

the eradication rate of the treatment regimen. Third, the analysis was confined to specific variables outlined in the study regarding their association with the VA and VAS regimens. Other potentially relevant factors influencing eradication rate —such as variations in the CYP3A4/5 enzymes responsible for P-CAB metabolism—were not examined.

From a clinical perspective, the high eradication rate achieved with the VAS regimen offers patients who have experienced previous treatment failures a renewed opportunity for successful cure, thereby reducing psychological distress associated with repeated failure. Additionally, the simplified VAS regimen reduces the economic burden and adverse events on patients and ensures high treatment adherence.

Conclusion

S. boulardii supplementation in the VA dual therapy significantly enhances the *H. pylori* eradication rate while concurrently decreasing the incidence of adverse events. This is a safe, good compliance, and simplified rescue therapy independent of the number of prior failed treatments. However, prior use of furazolidone reduced the eradication rate, although this finding should be interpreted cautiously due to the small subgroup size. Future research will involve large-scale, multicenter randomized controlled trials to validate these findings further.

Data Sharing Statement

All data and materials generated during the study can be availed by the corresponding author upon reasonable request.

Ethics Statement and Consent to Participate

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Nanjing Medical University [No. (2023) YLJSA017]. It also adhered to the principles of the Declaration of Helsinki. All study participants provided informed written consent before study enrollment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no conflicts of interest regarding this work.

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