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# Efficacy of a 7-day vonoprazan, sitafloxacin, and amoxicillin triple therapy as a fourth-line salvage regimen for refractory *Helicobacter pylori* infection

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## Abstract

**Background** Treatment failure of three standard regimens for *Helicobacter pylori* infections has increased and represents a significant challenge. The VAS regimen, consisting of vonoprazan, amoxicillin, and sitafloxacin, represents a promising treatment option, supported by its strong acid suppression and broad-spectrum antimicrobial activity.

**Objectives** To evaluate the efficacy and safety of the VAS regimen as the fourth-line regimen for refractory *H. pylori* infection.

**Methods** This prospective single-arm study involved patients with *H. pylori* infection who had failed three standard regimens. Participants received VAS regimen; comprising vonoprazan 20 mg twice daily, amoxicillin 1000 mg twice daily, and sitafloxacin 100 mg twice daily for 7 days. Genotypic resistance was identified and CYP2C19 and CYP3A5 were studied. Eradication success was assessed using the 13C-urea breath test at 4-8 weeks post-therapy.

**Results** Twenty patients (mean age 64.4 ± 8.6 years) were enrolled. The eradication rate was 70.0% (95% confidence interval (CI): 45.7–88.1) in the intention-to-treat analysis and 68.42% (95% CI: 43.5–87.4) in the per-protocol analysis. Notably, genotypic resistance demonstrated 93.9% and 85.7% of levofloxacin and clarithromycin resistance respectively. Mild adverse events were reported by three patients (15%), including loose stools, nausea, and bloating. Neither antibiotic resistance nor CYP2C19 and CYP3A5 rapid metabolizer status was associated with eradication failure.

**Conclusion** The seven-day VAS regimen was well tolerated and demonstrated acceptably good efficacy as the fourth-line treatment for refractory *H. pylori* infection. The regimen offers a reasonably viable empirical rescue when lack of antibiotic susceptibility testing.

**Trial registration** Thai Clinical Trials Registry (Identifier: TCTR20211203002, December 3, 2021).

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**Keywords** *Helicobacter pylori*, Vonoprazan, Sitafloxacin

## Introduction

*Helicobacter pylori* infection affects approximately 40% of the global population [1] and is linked to several gastrointestinal disorders, including gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [2]. The efficacy of first-line treatment regimens has declined to 80–90% [3]. Refractory *H. pylori* infection, which necessitates more than three treatment courses, has a prevalence of 2–3% [4, 5]. Treatment failure is primarily due to poor treatment compliance, an increase in resistant strains of *H. pylori*, and insufficient acid suppression [6].

The updated international *H. pylori* treatment guidelines recommend the three first line treatments including clarithromycin-based regimens (both sequential and concomitant), levofloxacin-based triple therapy, and bismuth quadruple therapy [7–9]. Antibiotic susceptibility test-guided treatment was advocated by some guidelines after two or three treatment failures. Unfortunately, such testing is limited in availability and practicality in many regions. Complicated gastric tissue specimen collection, transport, and culture processes are the main hurdles given the fastidious nature of *H. pylori* [6, 10]. Studies indicated that empirically selected treatment based on prior antibiotic exposure can be as effective as those guided by antibiotic susceptibility tests [11]. Therefore, empirical treatment approaches are commonly employed in real-world settings.

Several regimens have been proposed for refractory *H. pylori* infection, including rifabutin-based triple therapy, high-dose dual therapy, and sitafloxacin-based triple therapy. The regimen combining vonoprazan, amoxicillin, and sitafloxacin (VAS regimen) leverages two mechanisms to enhance the efficacy of *H. pylori* eradication. Firstly, vonoprazan, a potassium-competitive acid blocker, exhibits advantages over traditional proton pump inhibitors (PPIs) given its potent acid suppression, rapid onset and prolonged stability in acidic environments [12]. The potency of acid suppression is critical to maximize the efficacy and sustained activity of antibiotics and proliferation of *H. pylori*, which is crucial for the action of certain antimicrobial agents [13]. Secondly, sitafloxacin is a broad-spectrum antibiotic that is infrequently used, providing a benefit for patients who failed to prior antibiotic exposure. Levofloxacin and sitafloxacin, categorized in quinolones group still demonstrated effective results in patients with prior exposure and failed to levofloxacin [14]. Specifically, vonoprazan provides rapid and sustained acid suppression starting from the first dose, whereas conventional PPIs typically require 4–5 doses to achieve comparable acid inhibition [12]. This early and potent acid suppression allows antibiotics to be effective from the beginning of therapy, supporting the use of a shorter treatment duration. In addition, two randomized controlled trials have demonstrated that the eradication efficacy of sitafloxacin-based triple therapy was not significantly different between 7- and 14-day regimens [15]as well as between 7- and 10-day regimens [16]. Meta-analysis indicated that VAS regimen achieves 87.5% (95% confidence interval (CI): 73.3–94.7%) eradication rate as a third-line treatment [17]. However, data on its efficacy as a fourth-line treatment are scarce.

This study aims to evaluate the efficacy of the empirical VAS as the fourth-line rescued regimen in patients who failed three prior standard eradication. Patient characteristics, including genotypic antibiotic resistance and drug metabolism polymorphisms were explored.

## Methods

### Study design and study population

This is a single-arm prospective interventional study, conducted at Siriraj Hospital, a tertiary care center in Bangkok, Thailand. Adult patients (age > 18 years) who failed three regimens of *H. pylori* eradication were enrolled after obtaining written informed consent. Three unsuccessful regimens included a clarithromycin-based regimen—either sequential regimen (PA-PMC: PPIs, amoxicillin for the first 5–7 days followed by PPIs, clarithromycin, metronidazole for the subsequent 5–7 days) or a concomitant regimen (PAMC: PPIs, amoxicillin, metronidazole, clarithromycin for 10–14 days) as the first regimen. The second regimen involved either bismuth quadruple therapy (PBMT: PPIs, bismuth, metronidazole, tetracycline for 14 days) or a levofloxacin-based triple regimen (PAL: PPIs, amoxicillin, levofloxacin for 14 days). The third regimen alternated between PBMT or PAL, whichever has not been administered as the second treatment. Eradication failure was documented by a positive urea breath test (UBT). The exclusion criteria included a history of allergic to vonoprazan, amoxicillin, or sitafloxacin. Pregnant or breastfeeding women were excluded.

### Human ethics and consent to participate declarations

The study has been approved by the Siriraj Institutional Review Board of Human Research Protection Unit, Faculty of Medicine Siriraj hospital (certificate of approval number Si 982/2020). All eligible participants were invited, and written informed consents were obtained after receiving detailed information about the study. The study was registered in the Thai Clinical Trials Registry (Identifier: TCTR20211203002, December 3, 2021).

### Treatment protocol

The diagnosis of refractory *H. pylori* infection was made using a positive rapid urease test. During esophagogastroduodenoscopy (EGD), five gastric biopsy samples (two from the antrum, one from the incisura, and two from the body) were collected and sent for genotypic antibiotics resistance. Blood samples were taken for CYP2C19 and CYP3A5 genotyping testing. Patient characteristics, including demographic data, experienced antibiotics and medications use in the last year, and endoscopic findings, were documented. The prescribed regimen consisted of vonoprazan 20 mg twice daily, amoxicillin 1000 mg twice daily, and sitafloxacin 100 mg twice daily for one week. A follow-up visit was scheduled to assess eradication success. Adverse events and compliance were assessed and recorded. Intake of less than 80% of the prescribed medication was considered poor compliance.

### Confirm eradication

*H. pylori* eradication was confirmed by a negative result of 13C-urea breath test at 4–8 weeks after treatment completion. The cutoff value for a negative UBT was set at < 2.5%.

### Genotypic resistance

*H. pylori* strains were isolated from gastric biopsy specimens. The genomic DNA was extracted using the QIAamp DNA mini kit (Qiagen). Polymerase chain reaction (PCR) was performed using MyTaq™ Red Mix (Bioline) with standard protocol. Genes associated antibiotic resistance genes, including 23 S rRNA (for clarithromycin resistance), *gyrA* (for quinolone resistance), *pbp1A* (for amoxicillin resistance), 16 S rRNA (for tetracycline resistance), and *rdxA* (for metronidazole resistance) were amplified. PCR primers and mutation loci interpretation are provided in Table S1 [18–22]. All PCR amplicons were sequenced using the Sanger sequencing service provided by BNK Bioscience, Thailand.

### CYP2C19 and CYP3A5 genotyping

Genomic DNA was extracted from blood samples. Genotyping was carried out with a single-nucleotide polymorphism assay in a real-time polymerase chain reaction system. We analyzed polymorphisms in the CYP3A5*3 gene (rs776746, G > A) and the CYP2C19 gene, including three mutant alleles: CYP2C19 *2 (rs4244285, A/G), *3 (rs4986893, G/A), and *17 (rs12248560, A/C/T).

### Statistical analysis

Eradication rates were assessed through intention-to-treat (ITT) and per-protocol (PP) analyses, both presented as proportions with 95% confidence intervals (CIs). Patient characteristics were described, with categorical data reported as proportions. Continuous data were displayed as means ± standard deviation (SD) for normally distributed variables or medians with interquartile ranges (IQR) for non-normally distributed variables. Comparisons of categorical variables between treatment success and treatment failure groups were analyzed using Chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed using STATA Statistical Software, version 17.0 SE (StataCorp LLC, College Station, TX, USA).

## Results

### Patient characteristics

Among the 20 patients who were enrolled from January 2022 to January 2023, one developed angioedema and rash, leading to discontinuation of the medication on the 4$^{th}$ day of treatment. Consequently, 20 patients were included in the intention-to-treat (ITT) analysis and 19 in the per-protocol (PP) analysis (Fig. 1). The mean age of the participants was 64.40 ± 8.55 years, with 30% (6/20) male. Regarding CYP2C19 metabolism, ultra-rapid and rapid metabolizers were identified in 5% (1/20) and 60% (12/20) of the patients, respectively. Additionally, 10% (2/20) of the patients were classified as CYP3A5 rapid metabolizers. Further details on patient characteristics, including underlying diseases, presenting symptoms, and endoscopic findings, are provided in Table 1.

### Antimicrobial susceptibility testing

Of the 20 patients, 14 completed the evaluation for genotypic drug resistance. Among these, 85.7% (12/14) exhibited at least one mutation in the 23S rRNA gene associated with clarithromycin resistance. Additionally, 92.9% (13/14) displayed at least one mutation in the *gyrA* gene indicative of levofloxacin resistance, with one patient (7.1%) showing two mutations in the *gyrA* gene. Mutations in the pbp1A gene (amoxicillin resistance) were detected in 6 patients (42.9%), while mutations in the 16S rRNA gene (tetracycline resistance) were observed in 3 patients (21.4%). The rdxA gene, associated with metronidazole resistance, was mutated in 13 patients (92.9%). Full details are shown in Table 2.

### Eradication rate

All patients, except for one who developed an allergic reaction, achieved 100% of treatment compliance. The eradication rate was 70% (14/20; 95% CI = 45.72–88.10) in the intention-to-treat (ITT) analysis and 68.42% (13/19; 95% CI = 43.45–87.42) in the per-protocol (PP) analysis (Fig. 2).

### Adverse events

Three patients reported adverse events, including diarrhea, bloating, and nausea, each symptom in each

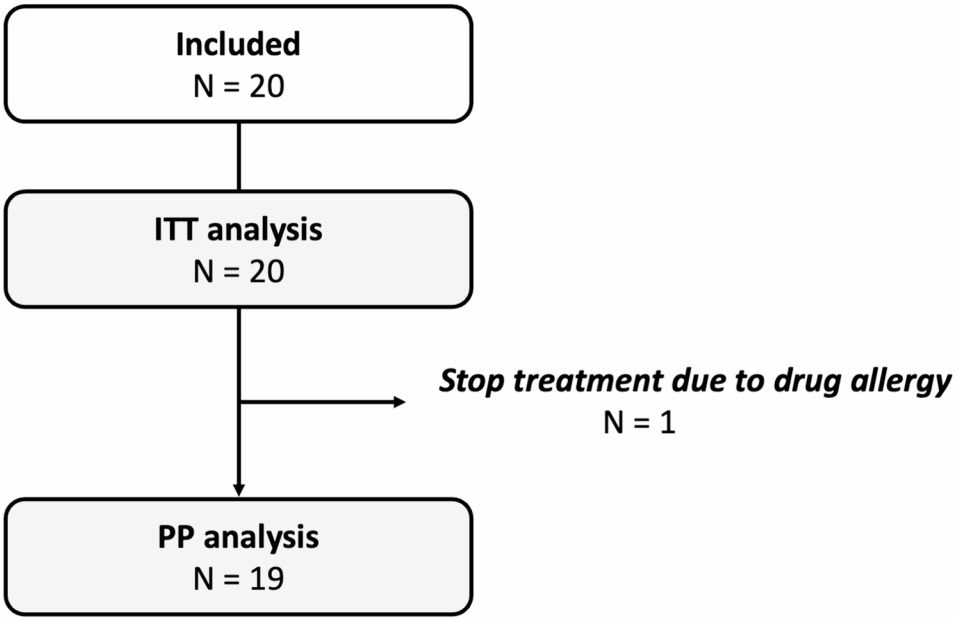


**Fig. 1** Flow diagram of the study ITT; intention-to-treat, PP; per protocol

**Table 1** Patients characteristics

| Parameters | N=20 |
|---|---|
| Age, mean ± SD (years) | 64.40 ± 8.55 |
| Male, n (%) | 6 (30) |
| BMI, mean ± SD (kg/m$^2$) | 23.48 ± 3.80 |
| Smoking, n (%) | 2 (10) |
| Comorbidity, n (%) | |
| Diabetes | 6 (3) |
| Hypertension | 9 (45) |
| Coronary artery disease | 1 (5) |
| Chronic kidney disease | 1 (5) |
| Pre-treatment symptoms, n (%) | |
| Asymptomatic | 12 (60) |
| Epigastric pain | 2 (10) |
| Post prandial distress | 4 (20) |
| Bloating | 2 (10) |
| Endoscopic finding, n (%) | 10 (5) |
| Non-erosive gastropathy | |
| Erosive gastropathy | 3 (15) |
| Hemorrhagic gastropathy | 5 (25) |
| Nodular gastropathy | 1 (5) |
| Gastroduodenal ulcer | 1 (5) |
| CYP2C19 genotype, n (%) | |
| Ultra-rapid metabolizer (*1/*17) | 1 (5) |
| Rapid metabolizer (*1/*1) | 12 (60) |
| Intermediate metabolizer (*1/*2, *1/*3) | 6 (30) |
| Poor metabolizer (*2/*2) | 1 (5) |
| CYP3A5 genotype, n (%) | |
| Rapid metabolizer (*1/*1) | 2 (10) |
| Intermediate metabolizer (*1/*3) | 13 (65) |
| Poor metabolizer (*3/*3) | 5 (25) |

*BMI* Body mass index, *SD* Standard deviation

**Table 2** Prevalence of genotypic drug resistance

| Gene mutations | N=14 (%) |
|---|---|
| 23S rRNA (clarithromycin resistance) | 12 (85.7) |
| *gyrA* (quinolone resistance) | 13 (92.9) |
| One locus mutation | 12 (85.7) |
| ≥ Two loci mutation | 1 (7.1) |
| *pbp1A* (amoxicillin resistance) | 6 (42.9) |
| 16S rRNA (tetracycline resistance) | 3 (21.4) |
| *rdxA* (metronidazole resistance) | 13 (92.9) |

individual patient, as detailed in Table 3. All adverse events were mild to moderate degree.

#### Factors associated with treatment outcome

The characteristics of patients with treatment success and treatment failure following the VAS regimen were not significantly different (Table 4). Smoking was reported in 1 of 14 patients in the treatment success group and in 1 of 6 patients in the treatment failure group. CYP2C19 rapid or ultra-rapid metabolizer phenotype was identified in 8 of 14 patients with treatment success and in 5 of 6 patients with treatment failure. CYP3A5 rapid metabolizer status was observed in 1 patient in each group.

Among the 14 patients who underwent genotypic resistance testing, clarithromycin resistance was detected in 8 of 9 patients with treatment success and in 4 of 5 patients with treatment failure. Levofloxacin resistance at one or more loci was found in 8 of 9 patients with treatment success and in 4 of 5 patients with treatment failure. Dual-locus mutations in gyrA were observed in 1 of 5 patients with treatment failure, but in none of the patients with treatment success. Full details are provided in Table 4.

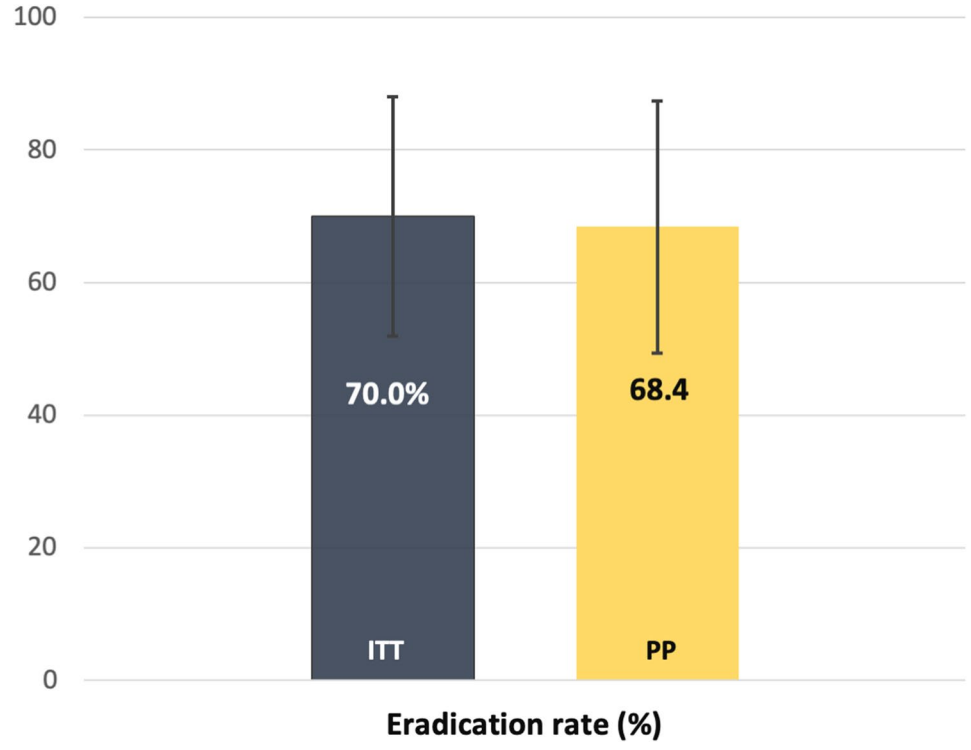


**Fig. 2** Eradication rate of VAS regimen ITT; intention-to-treat ($n=20$), PP; per protocol ($n=19$)

**Table 3** Adverse events of VAS regimen

| Adverse events | N =20 (%) |
|---|---|
| Diarrhea | 1 (5) |
| Bloating | 1 (5) |
| Abdominal pain | 0 |
| Nausea | 1 (5) |
| Dysgeusia | 0 |
| Headache | 0 |
| Belch | 0 |
| General malaise | 0 |

**Table 4** Factors associated with VAS regimen eradication failure

| Factors | Eradication rate (*n*/*N*, %) | | *P*-value |
|---|---|---|---|
| | Factor present | Factor Absence | |
| Smoking | 1/2 (50.0) | 13/18 (72.2) | 0.521 |
| CYP2C19 rapid or ultra-rapid metabolizer | 8/13 (61.5) | 6/7 (85.7) | 0.354 |
| CYP3A5 rapid metabolizer | 1/2 (50.0) | 13/18 (72.2) | 0.521 |
| Clarithromycin resistance | 8/12 (66.7) | 1/2 (50.0) | 1.000 |
| Quinolone resistance (1 locus) | 8/13 (61.5) | 1/1 (100) | 1.000 |
| Quinolone resistance (≥ 2 loci) | 0/1 (0) | 9/13 (69.2) | 0.357 |
| Amoxicillin resistance | 2/6 (33.3) | 7/8 (87.5) | 0.091 |
| Tetracycline resistance | 1/3 (33.3) | 8/11 (72.7) | 0.505 |
| Metronidazole resistance | 8/13 (61.5) | 1/1 (100) | 1.000 |

## Discussion

Our study has presented a practical regimen of a 7-day vonoprazan, amoxicillin, and sitafloxacin (VAS) as a fourth-line therapy for refractory *H. pylori* infection, with a reasonably good response with 70% eradication rate. This efficacy is attributable to the potent acid suppression provided by vonoprazan, and the broad-spectrum antibiotic activity of sitafloxacin. Additionally, the short course and simplicity of the regimen, as well as minimal side effects fostered excellent compliance among participants.

The studied cohort represents typical patients with refractory *H. pylori* infection, previously failed three standard regimens (PA-PMC or PAMC, PAL, and PBMT). Notably, this cohort had a significant proportion of rapid and ultra-rapid metabolizers of CYP2C19 (65%), which is higher than the general Thai population (45%) [23]. The CYP2C19 genotype is a well-known influence on PPIs metabolism, resulting in decrease of acidic environments and compromised the efficacy of various antibiotics like amoxicillin, tetracycline, and clarithromycin [24]. The superiority of vonoprazan to PPIs which partly from its CYP2C19-independent metabolism. Given that *H. pylori* thrives within a narrow pH range and is susceptible to growth-dependent antibiotics [25]vonoprazan may compensate the reduction of PPIs efficacy.

Furthermore, the prevalence of genotypic resistance to levofloxacin in our sample was extremely high up to 80%. Patients with *H. pylori* which prior failed levofloxacin

containing regimen finally can successfully response to sitafloxacin. This suggests that it could be a viable option as it requires double mutations in *gyrA* for resistance to manifest [14, 26]aligning with our findings where successful treatment was observed even with a single *gyrA* mutation. Furthermore, data from a 2022 systematic review of third-line regimens demonstrated that sitafloxacin-based triple therapy (e.g., sitafloxacin–amoxicillin combined with rabeprazole or vonoprazan) achieved overall eradication rates ranging from 50 to 90%, even among patients previously treated with levofloxacin [27].

Patients who failed clarithromycin- and levofloxacin-based regimens typically exhibit high resistance to these antibiotics, consistent with our findings of clarithromycin and levofloxacin resistance rates of 85.7% and 93.9%, respectively. In contrast, amoxicillin resistance is usually low worldwide, generally < 5% even among patients with multiple prior treatment failures [28]. Unexpectedly, our study observed a substantially higher prevalence of amoxicillin resistance (42.9%). When eradication outcomes were stratified by amoxicillin susceptibility, the eradication rate was markedly lower in resistant cases (33.3%) compared with susceptible cases (87.5%). These findings suggest that, although vonoprazan and sitafloxacin provide potent acid suppression and broad-spectrum antibacterial coverage, the presence of amoxicillin resistance can significantly influence treatment success. Such data emphasize that amoxicillin resistance, though generally rare, should not be overlooked, particularly in patients with multiple prior treatment failures.

Comparatively, the efficacy of VAS regimen appears to be similar to the other available fourth-line treatments, such as rifabutin-based regimens, which have an eradication rate of 70% (95%CI 60–79%) from meta-analysis [29]. However, our regimen exhibited fewer side effects, indicating a better tolerance profile.

Despite vonoprazan being metabolized via CYP3A4/5, we found neither significant association between CYP3A5 rapid metabolizer status nor treatment failure, which is consistent with current literature [30]. The mechanisms underlying this observation remain unclear and warrant further investigation with a larger population.

In clinical setting, antibiotic susceptibility testing is challenging given the complexity of *H. pylori*'s cultivation. However, evidence suggests that antibiotic selection based on prior antibiotic exposure is probably as effective as susceptibility test-guided therapy [11]. supporting the use of the VAS regimen as an empirical treatment where susceptibility test is not feasible.

The strength of this study lies in addressing the clinical challenge presented by patients who failed three treatment regimens, which is not uncommon. We also provide a comprehensive analysis of both CYP2C19 and CYP3A5 polymorphisms and genotypic antibiotic resistance, thereby contributing to the understanding of treatment refractoriness and informing future research directions.

This study has some limitations. First, the relatively small sample size may have limited our ability to demonstrate associations between certain resistance factors and treatment outcomes, such as quinolone and amoxicillin resistance. Larger studies are warranted to clarify these relationships. Additionally, phenotypic susceptibility testing could not be performed due to sample transport restrictions during the COVID-19 pandemic. Although genotypic resistance testing does not always fully reflect in vivo phenotypic resistance, previous metaanalyses and recent studies have demonstrated good correlation between genotypic and phenotypic resistance for clarithromycin and quinolones, although the correlation is weaker for other antibiotics [31, 32]. Nevertheless, genotypic testing is more practical and widely accessible, and we believe our findings remain clinically relevant and pragmatically applicable.

In conclusion, The VAS regimen is effective and safe as a fourth-line treatment option for refractory *H. pylori* infection. Its simplicity and shorter treatment duration make it a practical option for empirical treatment where the antibiotic susceptibility testing is limited.

**Abbreviations**

| | |
|---|---|
| ACG | American College of Gastroenterology |
| CI | Confidence Interval |
| DNA | Deoxyribonucleic Acid |
| EGD | Esophagogastroduodenoscopy |
| gyrA | DNA gyrase subunit A |
| ITT | Intention–To–Treat |
| IQR | Interquartile Range |
| MALT | Mucosa–Associated Lymphoid Tissue |
| PCR | Polymerase Chain Reaction |
| PBMT | PPI, Bismuth, Metronidazole, Tetracycline |
| PAMC | PPI, Amoxicillin, Metronidazole, Clarithromycin |
| PA-PMC: | PPI, Amoxicillin then PPI, Metronidazole, Clarithromycin |
| PAL | PPI, Amoxicillin, Levofloxacin |
| PP | Per Protocol |
| PPI(s) | Proton Pump Inhibitor(s) |
| R2R | Routine to Research |
| rRNA | Ribosomal Ribonucleic Acid |
| SD | Standard Deviation |
| UBT | Urea Breath Test |
| VAS | Vonoprazan, Amoxicillin, Sitafloxacin |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04226-x.

Supplementary Material 1.

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**Authors' contributions**
Study conception and design: M.M., T.G., S.L., W.K., I.T., S.T., C.L. Data collection: T.G., T.A. Investigation: T.G., T.A., P.C., W.L., S.T. Data analysis and interpretation of results: T.G., M.M., S.T. Draft manuscript preparation: T.G., M.M., S.T. All authors reviewed the results and approved the final version of the manuscript.

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**Data availability**
The data supporting this study's findings are available from the corresponding author upon request.

## Declarations

**Ethics approval and consent to participate**
This study was conducted in accordance with the ethical principles outlined.

**Consent for publication**
Not Applicable.

**Competing interests**
The authors declare no competing interests.

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