

Combinations of antibiotics and vonoprazan for the treatment of *Helicobacter pylori* infections—Exploratory study

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Abstract

Background: Vonoprazan fumarate is a novel potassium-competitive acid blocker more effective in suppressing acid production than proton pump inhibitors (PPIs) and when combined with antibiotics has been used to eradicate *Helicobacter pylori* (*H. pylori*) infection. However, it has not yet been examined in an Australian setting. This study aimed to report on the efficacy and safety of vonoprazan-containing antibiotic combination therapies in the eradication of *H. pylori*.

Methods: A single-center, exploratory, clinical review of patients 18 years or over, positive for *H. pylori* on Urea Breath Test (UBT), and/or histopathology who underwent a 10-day treatment of combination antibiotics plus vonoprazan between January 2017 and September 2019 was conducted. Eleven different combinations of antibiotics that included 2–5 different antibiotics predominantly amoxicillin, rifabutin, levofloxacin, furazolidone, nitazoxanide, and tetracycline were included. The eradication success was based on negative UBT results and/or histopathology results after the treatment. Descriptive statistics were summarized.

Results: One hundred and fifty-three patients (Female $n = 74$, 48%) with a positive for *H. pylori* were treated with vonoprazan-containing antibiotic combination therapy during the study period. Of the 153 patients, 48 (31%) had previously failed a PPI-based *H. pylori* treatment. Follow-up was available for 66/153 (43%) patients. In those who completed follow-up, overall eradication was achieved in 97% (64/66) of patients. In the subgroup of patients treated for the first time, eradication was achieved in 100% (44/44). In those who had failed prior, non-vonoprazan-containing treatment, eradication was achieved in 91% (20/22) of patients.

Conclusions: Vonoprazan-containing antibiotic therapy is an effective *H. pylori* eradication treatment. It is capable of achieving 100% efficacy in patients treated for the first time and even 91% efficacy in patients with previous eradication failure. Subsequent studies utilizing a factorial design will be needed to optimize each regimen as most regimens contained more than two antibiotics.

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KEYWORDS

antibiotics, *Helicobacter pylori*, potassium-competitive acid blockers, proton pump inhibitors, urea breath test

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium, which can reside in the gastric mucosa.^{1,2} *H. pylori* infection affects nearly half of the population worldwide.³ In Australia, 25%–30% of the population are infected, with prevalence increasing with age.⁴ *H. pylori* infection is a common cause of histologic gastritis, which is strongly linked to peptic ulcer disease.⁵ The ability of *H. pylori* to colonize the human gastric mucosa is largely dependent on the virulence of the bacterium.⁶ Gastric pH level, the integrity of the gastric mucosal layer, and the immune response to the infecting bacterium are some of the several patient and environmental factors that may also be involved in determining the virulence of *H. pylori* and may play a role in the progression of the disease. Historically, smoking, alcohol consumption, and regular use of non-steroidal anti-inflammatory (NSAIDs) drugs were thought to contribute to the development of peptic ulcer disease (PUD).^{7–9} Once established, *H. pylori* infection induces an inflammatory response of acute then chronic gastritis which can progress to a peptic ulcer if not eradicated.¹⁰

Helicobacter pylori is classified as a Class 1 carcinogen by the World Health Organization's International Agency for Research on Cancer, causing gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.¹¹ Early and successful treatment of the infection has been shown to prevent surgical procedures caused by PUD and significantly reduce PUD death rate and overall medical costs, which in Australia have been calculated to be some \$10.03 billion over 17 years.^{12,13}

During the 19th century, peptic ulcers were treated with antacids and gastric acid suppressors including milk and cream hourly, aluminum hydroxide, bismuth salts, deglycyrrhizinated licorice, magnesium carbonate, and sodium bicarbonate drug combinations.¹⁴ Later, H₂ receptor antagonists, such as Cimetidine, were marketed.^{15,16} Following the discovery of the causal relationship between *H. pylori* infection and PUD, treatments began to incorporate antibiotics in order to clear the underlying infection. The first effective treatment involving antibiotics for *H. pylori* marketed as Helidac and often referred to as “triple therapy” was developed in the 1980s at this clinic and was comprised of bismuth, tetracycline, and metronidazole.¹⁷ Later, antibiotics were combined with a proton pump inhibitor (PPI) to enhance the effect of antibiotics.¹⁸ Esomeprazole, a PPI, combined with clarithromycin and amoxicillin (Nexium Hp7) has been the first-line treatment for *H. pylori* since 2010. However, due to emerging clarithromycin resistance, the efficacy of Nexium Hp7 has plummeted such that it has now been recommended that Nexium Hp7 use be limited.^{19–21} One study reported that primary and secondary clarithromycin resistance to *H. pylori* were 7.4% and 78.7% respectively in Australia.²² This development has demanded the search for a more effective treatment.

Vonoprazan is a new potassium-competitive acid blocker used in the treatment of gastric or duodenal ulcer disease in Japan.^{23,24}

Vonoprazan suppresses acid secretion, though it is not a PPI, but functions similarly through the inhibition of the H⁺, K⁺ ATPase enzyme in gastric parietal cells.²⁵ Vonoprazan has greater power to elevate gastric pH than PPIs due to its ability to rapidly inhibit and maintain suppression of gastric acid secretion.^{26–28} A recent systematic review and meta-analysis showed that vonoprazan-containing antibiotic therapy was superior to other PPI-containing therapies for *H. pylori* with similar levels of side effects.²⁹ One randomized controlled trial, also conducted in Japan, found that vonoprazan-containing antibiotic therapy was superior to conventional PPI-containing antibiotic therapy for both first-line and second-line treatment for eradication of *H. pylori* infections due to improved efficacy.³⁰ Vonoprazan can also improve the eradication of clarithromycin and metronidazole-resistant *H. pylori* strains.^{31,32}

Graham et al.³³ showed an 83% cure rate using a 14-day rifabutin, omeprazole, and amoxicillin combination, which had been the standard in our Clinic prior to 2016. However, our patients repeatedly achieved a successful eradication when omeprazole was changed to vonoprazan, which further points to vonoprazan as being an important factor in increasing eradication efficacy.

Therefore, the purpose of this study is to report on the efficacy and safety of vonoprazan-containing triple therapy as first-line treatment within the Australian clinical setting as well as personalized antibiotic combinations for eradication of *H. pylori* in those with numerous previous failed treatments.

2 | METHODS

2.1 | Study design

A single-center, retrospective observational clinical review of patients who received vonoprazan-containing treatment for *H. pylori* between January 2017 and September 2019 was conducted. Included were patients who received vonoprazan-containing treatment aged 18 years or over with a positive diagnosis of a *H. pylori* infection established through histopathology of a gastric biopsy or a urea breath test (UBT) if histopathology was unavailable.

Between 2017 and 2019, several vonoprazan-containing treatment combinations for *H. pylori* were used at our center to accommodate various allergies to antibiotics and previous treatment failures. The most common treatment, predominantly used in cases of a single previous treatment failure, was comprised of vonoprazan 20 mg, amoxicillin 1125 mg, and rifabutin 80 mg three times a day for 10 days. Taking into account patient allergies and both the number and kind of previous eradication failures (maximum of 8 recorded), the compositions of vonoprazan-containing therapies were personalized by the treating physician. Hence, 11 different combinations that included 2–5 antibiotics plus vonoprazan with or

TABLE 1 A Vonoprazan-based treatment regimens ($n > 5$) and eradication of *Helicobacter pylori* (Total $n = 138$).

Regimen	Treatment	Day 1		Day 2		Day 3-10		Description of previous treatment failed/not failed	No Follow-up (n)	Successful <i>H. pylori</i> eradication (n)	Unsuccessful eradication (n)	Adverse events reported (n)
		mg/ b.i.d	mg/t.i.d	mg/ b.i.d	mg/t.i.d	mg/b.i.d	mg/t.i.d					
#1	Vonoprazan	20	20	20	20	20	20	Total	63	37 (97%)	1 (3%)	2 (5%)
N = 101	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	79	29	0	
	Rifabutin	50	60	60	80	80	80	Failed \geq once	22	8	1	
#2	Vonoprazan	20	20	20	20	20	20	Total	14	7 (100%)		4 (57%)
N = 14	Levofloxacin	375	375	375	375	375	375	Not failed	7	5		
	Rifabutin	180	60	60	120	120	300	Failed \geq once	7	2		
	Bismuth	300	300	300	300	300	300		5	2		
#3	Vonoprazan	20	20	20	20	20	20	Total	23	14 (100%)		5 (36%)
N = 23	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	15	9		
	Levofloxacin	375	375	375	375	375	375	Failed \geq once	8	5		
	Rifabutin	60	60	60	120	120			3			
	Furazolidone	100	100	100	100	100	100					
	Nitazoxanide	500	500	500	500	500	500					
	Bismuth	300	300	300	300	300	300					

b.i.d, two times a day; t.i.d, three times a day; F/U, Follow-up; mg, milligram.

TABLE 1B Vonoprazan-based treatment regimens ($n < 5$) and eradication of *Helicobacter pylori* (Total $n = 15$).

Regimen	Treatment	Day 1		Day 2		Day 3-10		Description of previous treatment failed/not failed	No Follow-up (n)	Successful <i>H. pylori</i> eradication (n)	Unsuccessful eradication (n)	Adverse events reported (n)
		mg/b.i.d	mg/t.i.d	mg/b.i.d	mg/t.i.d	mg/b.i.d	mg/t.i.d					
#4	Vonoprazan	20	20	20	20	20	20	Total	1	1		None
N = 1	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	0	0		
	Rifabutin	60	60	120	120	100	100	Failed ≥once	1	1		
	Furazolidone	500	500	500	500	300	300					
#5	Vonoprazan	20	20	20	20	20	20	Total	1	1		None
N = 1	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	0	0		
	Tetracycline	250	250	250	250	250	250	Failed ≥once	1	1		
	Rifabutin	60	60	120	120	300	300					
#6	Vonoprazan	20	20	20	20	20	20	Total	2	1	1 (100%)	None
N = 2	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	0	0		
	Tetracycline	250	250	250	250	250	250	Failed ≥once	2	1	1	
	Rifabutin	60	60	120	120	500	500					
	Nitazoxanide	500	500	180	180	300	300					
	Pronase	180	180	300	300	20	20	Total	4	2	2 (100%)	2 (100%)
#7	Vonoprazan	20	20	20	20	20	20	Total	4	2	2 (100%)	2 (100%)
N = 4	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	2	1	1	
	Tetracycline	250	250	250	250	250	250	Failed ≥once	2	1	1	
	Rifabutin	60	60	120	120	500	500					
	Nitazoxanide	500	500	200	200	300	300					
	Metronidazole	200	200	300	300	20	20	Total	1	1	1 (100%)	None
#8	Vonoprazan	20	20	20	20	20	20	Total	1	1	1 (100%)	None
N = 1	Tetracycline	250	250	250	250	250	250	Not failed	0	0		
	Rifabutin	60	60	120	120	180	180	Failed ≥once	1	1		
	Nitazoxanide	500	500	500	500	180	180					
	Pronase	180	180	300	300	180	180					

(Continues)

TABLE 1B (Continued)

Regimen	Treatment	Day 1		Day 2		Day 3–10		Description of previous treatment failed/not failed	No Follow-up (n)	Successful <i>H. pylori</i> eradication (n)	Unsuccessful eradication (n)	Adverse events reported (n)
		mg/b.i.d	mg/t.i.d	mg/b.i.d	mg/t.i.d	mg/b.i.d	mg/t.i.d					
	Bismuth	300	300									
#9	Vonoprazan	20	20	20	20	20	20	Total	3	2	1 (100%)	None
N = 3	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	1	1	0	
	Rifabutin	60	60	120	120	120	120	Failed ≥once	2	1	1	
	Furazolidone	100	100	100	100	100	100					
#10	Vonoprazan	20	20	20	20	20	20	Total	1	1		None
N = 1	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	1	1		
	Levofloxacin	375	375	375	375	375	375	Failed ≥once	0	0		
	Bismuth	300	300	300	300	300	300					
#11	Vonoprazan	20	20	20	20	20	20	Total	2	2	1 (50%)	None
N = 2	Amoxicillin	1125	1125	1125	1125	1125	1125	Not failed	0	0	0	
	Rifabutin	60	60	120	120	120	120	Failed ≥once	2	1	1	
	Bismuth	300	300	300	300	300	300					

b.i.d, two times a day; t.i.d, three times a day; F/U, Follow-up; mg, milligram.

TABLE 2 Patient demographics and characteristics

Characteristics	Vonoprazan-based treatment (n = 153)
Gender	
Male (%)	79 (51.6%)
Female (%)	74 (48.4%)
Age range (mean) years	18–82 (54.08)
Previous treatment	48 (31.0%)
Failed once	21 (43.8%)
Failed >1 time (2–8)	27 (56.2%)
Pre-treatment test	
Only UBT completed	58 (37.9%)
Only Histology completed	12 (7.8%)
UBT and Histology completed	83 (54.2%)
Post-treatment test	
Only UBT completed	62 (40.5%)
Only Histology completed	1 (0.6%)
UBT and Histology completed	3 (2%)
No follow-up	87 (56.9%)
Time follow-up tests [§] conducted	
UBT	
<100 days [range] (mean)	48 [30–97] (59.9)
100–365 days [range] (mean)	15 [106–183] (138.3)
>365 days [range] (mean)	2 [435–516] (475.5)
Histology	
<100 days [range] (mean)	1 [90]
100–365 days [range] (mean)	0
>365 days [range] (mean)	3 [516–580] (547.6)

§Some patients had both UBT and histology tests performed post-treatment which means they are counted twice here.

without bismuth were prescribed for a period of 10 days. (Tables 1A and 1B) Included antibiotics were amoxicillin, rifabutin, levofloxacin, furazolidone, nitazoxanide, and tetracycline. Rifabutin was used in almost all patients except in-group #10 (n = 1) (Table 1B). Patients were provided with their specific treatment protocol and were given the opportunity to read and discuss this with their treating physician prior to the commencement of the therapy.

De-identified clinical data were entered directly into an Excel database. Extracted data included demography, medical history, history of failed treatments for the current *H. pylori* infection, treatment combinations, histology reports, and pathology reports including UBT, the date of treatment commencement, and follow-up testing. Patients were excluded if either their histopathology or UBT test results were not available prior to the treatment or if their follow-up tests were conducted before 4 weeks after completing treatment, as recommended.³⁴ The proportion of patients with demographic data was summarized as numbers and percentages (Table 2).

Descriptive statistics (mean, percentage, and range) were calculated for demographic data, medical history, treatment type, histology, and pathology reports on patients who underwent treatment for *H. pylori* with vonoprazan plus antibiotics.

TABLE 3 Efficacy and safety of vonoprazan-based treatment

	Vonoprazan-based treatment (n = 66)
Eradication of <i>Helicobacter pylori</i>	
Successful eradication	64 (97%)
Unsuccessful eradication	2 (3%)
Adverse events [^] reported	
Yes	13 (20%)
No	53 (80%)

[^]See Appendix A for adverse events

TABLE 4 Eradication according to previous treatment in vonoprazan-based treatment

	Vonoprazan-based treatment (n = 66)
No previous treatment	n = 44
Successful eradication	44 (100%)
Unsuccessful eradication	0
Previously failed treatment ≥once	n = 22
Successful eradication	20 (91%)
Unsuccessful eradication	2 (9%)

3 | RESULTS

In this study, among 198 patients who received vonoprazan-containing treatment, 153 patients met the inclusion criteria. Of the 153 patients, 74 (48%) patients were female (Table 2). The mean age was 54 years (range 18–82 years). Eleven different personalized antibiotic regimens combined with vonoprazan were utilized. Bismuth was also received by 49 patients in 9 regimens (#2#8, #10, and #11) (Tables 1A and 1B). A third of patients had previously failed [n = 48 (31%)] earlier treatments; most commonly Nexium Hp7 [n = 29, (60%)]. Of those with previous failed treatments, 56% failed more than once, ranging between 2 and 8 times (Table 2). Most patients [n = 141 (92%)] completed a UBT prior to receiving treatment and more than half had a gastric biopsy taken [n = 95 (62%)] to confirm the presence of a *H. pylori* infection.

Following the completion of treatment, follow-up test results were available for 66 (43%) patients. Follow-up tests were conducted between 30 and 516 days after treatment, with 60% of the patients completing a test <100 days after treatment (Table 2).

The entire cohort had a 97% (95% CI [89.6%–99.5%]) eradication rate. Side effects were reported by n = 13 (20%) and included nausea, “flu-like” symptoms (headache, body ache, and fatigue), and oral and vaginal thrush (Table 3; Appendix A). Personalized vonoprazan-containing treatments and the eradication rates for each treatment regimen are shown in Tables 1A and 1B. The majority of the patients including those who failed a single previous treatment received regimen number 1 (vonoprazan, amoxicillin, and rifabutin), which had an overall eradication rate of 97%. Notably, eradication rates were 100% (95% CI [92%–100%]) for groups 2 and 8, which did not receive amoxicillin due to allergy but did contain vonoprazan. Treatment

regimen 1 had a low adverse event profile compared with treatment regimen numbers 2, 3, and 7, which proportionally showed more side effects compared to the other regimens (Tables 1A and 1B).

Next, patients' previous treatment failures were examined (Table 4). In patients not treated previously, eradication of *H. pylori* was 100%. Efficacy was slightly lower (91%) (95% CI [72.2%–98.4%]) in those who had previously failed treatment (Table 4).

4 | DISCUSSION

This study demonstrated a 97% efficacy of vonoprazan-containing therapies. The mean age of our cohort of 54 years reflects the age group with the highest prevalence of *H. pylori* infections in Australia.³⁶ To the best of our knowledge, this is the first report of vonoprazan-containing therapies in the eradication of *H. pylori* in Australia covering patients treated for the first time and those after previous eradication failure.

Vonoprazan-containing antibiotic regimens demonstrated high efficacy, reaching 44/44 (100%) eradication of the infection in patients never treated before. The regimens achieved above 91% cure for those who previously failed eradication treatment. Many (85%) patients received higher doses of amoxicillin (1125 mg t.i.d) and vonoprazan (20 mg t.i.d) than those that had been used amoxicillin (750 mg b.d) and vonoprazan (20 mg b.d) previously^{37,38} and could be responsible for the outcomes in those regimens. To our knowledge, our protocol's result is the highest first-line eradication rate and our findings are similar to the previously reported efficacy of vonoprazan-containing therapies for the eradication of *H. pylori*. This suggests that a higher dosage of vonoprazan than lower dosage may improve eradication efficacy.³⁹

Previous reports have shown that when vonoprazan-containing regimens were used in first-line and second-line treatment, eradication rates were between 83%–96% and 72%–96%, respectively.^{37,38} In addition, one study reported 100% eradication in 19 patients with two failed therapies before being treated with vonoprazan (20 mg), amoxicillin (750 mg), and rifabutin (150 mg) twice daily for 10 days.⁴⁰

In addition to the role of vonoprazan itself, the high efficacy achieved from the vonoprazan-containing therapies reported in this study compared to previously published literature may be due to several other factors including treatment duration, type of antibiotics used along with their relative dosages. In comparison with other methods of acid suppression, such as PPIs, vonoprazan has been shown to have both higher bioactivity and enhanced stability in an acidic environment.^{41–44} This enables it to elevate the pH of the stomach to near neutral, which both enhances antibiotic activity and increases the metabolic activity of *H. pylori*, making it more susceptible to antibiotics.³¹ Indeed, when comparing to a study which used a 14-day omeprazole, rifabutin, and amoxicillin combination therapy, the 10-day vonoprazan, rifabutin, and amoxicillin therapy utilized here achieved more than 10% increased efficacy.³³ Additional explanations for the high rates of efficacy observed within our cohort include the use of rifabutin in all but one patient. Resistance of *H. pylori* to rifabutin is rare,

and its use in combination with amoxicillin and pantoprazole has been shown to achieve eradication in 91% of patients with resistant *H. pylori* infections.^{45–47} Antibiotic resistance may have been the causal factor in patients who previously failed Nexium Hp7 treatment in our study, and subsequent successful treatment with the vonoprazan-containing treatments used here could be largely attributable to the use of rifabutin. Of note, a significant proportion of those patients who failed previous treatments received rifabutin and amoxicillin in conjunction with levofloxacin, furazolidone, nitazoxanide, or tetracycline depending on allergies and previous eradication attempts. In such cases, concern over the unnecessary use of additional antibiotics that may contribute to global resistance is legitimate since evidence suggests that the use of dual therapy (vonoprazan and amoxicillin) compared with triple therapy (vonoprazan, amoxicillin, and clarithromycin) can achieve similar eradication rates.⁴⁸ Without the presence of antimicrobial susceptibility testing however, it is difficult to say whether patients treated with additional antibiotics in our study would have achieved eradication with the use of rifabutin and amoxicillin alone, highlighting the need for antibiotic susceptibility testing in routine clinical practice.

Moreover, since this study is comprised of real-world clinical data outside of a RCT setting, several treatment protocol alterations were made by the treating physician depending on the clinical scenario. As a result, the antibiotics included in the regimens were quite heterogeneous. Overall, the personalized treatment approaches, when compared with studies utilizing a RCT setting, may have contributed to an inflated efficacy. Despite this, the results from this study suggest that personalized treatment approaches may be more efficacious than single treatment approaches, and that they may aid in the timely eradication of resistant infections, leading to improved patient outcomes.

Overall, adverse events were experienced by 20% of patients, which included diarrhea, nausea, vomiting, headache, dizziness, thrush, loss of appetite, abdominal discomfort (eg, cramps), wind, insomnia, and flu-like symptoms. However, due to the nature of our study, we could not pinpoint which drug or combination may have caused these side effects. Interestingly, a recent systematic review reported no differences in adverse events between vonoprazan and PPI treatment.³¹ It is therefore likely that the range of antibiotics used within the vonoprazan-containing treatments reported here contributed to most of the side effects observed rather than vonoprazan itself.

There are a number of limitations of this study. Firstly, due to the lack of a factorial design or control arm, we were not able to comment with certainty which component or components of each personalized vonoprazan-containing compositions most influenced eradication success. Therefore, most regimens contained more than two antibiotics and subsequent studies utilizing a factorial design will be needed to optimize each regimen. In addition, this study was a small retrospective study, so, we were unable to examine whether the treatment regimen was taken or ceased prematurely by patients because of side effects of the treatment or any other reasons. However, the treatment regimen was for a short period and no serious adverse events were reported. Another limitation

of our study was the lack of information on antibiotic resistance, which require mucosal cultures. The lack of eradication confirmation due to loss to follow-up in a considerable number of the patients was also a notable limitation, and therefore, the data shown here are per protocol and not intention to treat. Many patients may have returned to their general practitioner for the follow-up testing, but did not go to the trouble of having the UBT due to improved symptoms. Another limitation of our study was the variable duration time of follow-up UBT or gastric biopsy with one-third of patients completing their post-treatment tests >100 days after treatment cessation.

Nevertheless, the high eradication rates observed within this study, and indeed other studies alike, warrant further investigation of vonoprazan-containing antibiotic combinations in the eradication of *H. pylori* infection using dosing similar to ours. As stated by Graham et al. (2020) "a paradigm shift is required to abandon current approaches and embrace antimicrobial stewardship, and therefore reliably achieve high cure rates."⁴⁹ Given the increasing microbial resistance, first-line therapies approaching 100% cure will minimize the need for rescue therapies.⁵⁰

5 | CONCLUSIONS

This study demonstrated that vonoprazan-containing therapy in an Australian setting is highly effective in eradicating *H. pylori*. It achieved 100% efficacy as first-line treatment and 91% effectiveness in those with previous eradication failures. High first-line efficacy with vonoprazan-containing therapy could largely prevent re-treatment, avoiding the development of antibiotic-resistant strains.

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DISCLOSURES

TJB has a pecuniary interest in the Centre for Digestive Diseases in Australia and reports research grant funds from Finch Therapeutics, USA. TJB's patents for *H. pylori* treatment combinations: filed: WO2019071290, AU2018348777, CA3049033, CN201880014978.X, EP18865750.6, NZ754962, US16/451781, ZA201904387, and AU2020050384; pending: US20190314355, CN110366415, and EP3551186; granted: US6489317-B1, US9050263-B2, AU762890-B2, CA2330424-C, and WO0203065-A1. AWG, AC, AJM, MVD, JT, and HH have no disclosures.

AUTHOR CONTRIBUTIONS

TJB, AWG, HH, and AC contributed to conceptualization of the project. TJB oversaw the project and provided supervision. TJB and JT collected clinical data. MVD, AJM, AC, AWG, and HH coordinated the project. AJM, AWG, and HH collected and collated the data. AWG and HH conducted the data analysis and drafted the

manuscript. AWG, HH, and AC provided support for data analysis and interpretation. All authors reviewed and edited the manuscript, and issued the final approval of the submitted version.

ETHICS APPROVAL

Ethical approval for this study was obtained from the institutional ethics committee (ethics approval no: CDD19-C05). This study was carried out in accordance with the procedure set out in this study protocol, good clinical practice (GCP) guidelines, and legal and regulatory requirements were met.³⁵ All patients provided written informed consent for off-label vonoprazan-containing antibiotics treatment. Vonoprazan was provided by a Compounding Pharmacy.

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APPENDIX A

Adverse effects in the vonoprazan-containing treatment.

A	Joint pain, flu-like symptoms
B	Nausea, diarrhea, and urine discoloration
C	Flu symptoms
D	Insomnia, head aching, back, chest, and lower abdominal pain—flu-like illness
E	Tiredness, nausea, flu-like symptoms, diarrhea, dizziness and oral thrush
F	Urine discoloration, diarrhea
G	Insomnia, head aching, back, chest, and lower abdominal pain—flu-like illness
H	Diarrhea, thrush, skin rash
I	Diarrhea
J	Nausea, metallic taste in mouth, discolored urine, vaginal thrush
K	Hot flushes
L	Flu symptoms, swelling of the hands, vaginal thrush
F	Bloating, stomach pain, head aching, skin rashes, vomiting