Case Reports in Gastroenterology

Case Rep Gastroenterol 2024;18:386–394
DOI: 10.1159/000540185
Received: April 22, 2024
Accepted: June 20, 2024
Published online: July 31, 2024

Single Case

Case Study of a Refractory Idiopathic Peptic Ulcer in Which 24-h Intragastric pH Monitoring Contributed to Its Pathophysiological Analysis

Tomoyo Iwano[a] Tsutomu Takeda[a] Shotaro Oki[a] Yasuko Uemura[a] Momoko Yamamoto[a] Ryota Uchida[a] Hisanori Utsunomiya[a] Daiki Abe[a] Nobuyuki Suzuki[a] Atsushi Ikeda[a] Yoichi Akazawa[a] Kumiko Ueda[a] Hiroya Ueyama[a] Mariko Hojo[a] Akihito Nagahara[a, b]

[a]Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan;
[b]Department of Pathophysiological Research and Therapeutics for Gastrointestinal Diseases, Juntendo University, Tokyo, Japan

Keywords
Idiopathic peptic ulcer · Misoprostol · Potassium competitive acid blocker · 24-h intragastric pH monitoring

Abstract
Introduction: In recent years, the frequency of idiopathic peptic ulcers (IPUs) has increased. However, the clinicopathological characteristics of IPU have not been fully elucidated and treatment methods for recurrent and refractory cases have not yet been established. ***Case Presentation:*** A man in his forties complained of epigastric discomfort. Esophagogastroduodenoscopy revealed a gastric ulcer in the lesser curvature of the gastric angle. After *Helicobacter pylori* was eradicated, the gastric ulcer recurred despite the administration of a potassium competitive acid blocker (PCAB), and a diagnosis of IPU was made. Twenty-four-hour intragastric pH monitoring revealed insufficient gastric acid suppression. Misoprostol was added to the patient's treatment. Subsequently, the ulcer healed and recurrence was not observed. ***Conclusion:*** For refractory IPU, the evaluation of pathophysiological function through 24-h gastric pH monitoring may lead to the selection of an appropriate treatment. If a proton pump inhibitor and PCAB do not improve the IPU, combination treatment with misoprostol may be considered as an option.

Correspondence to:
Tsutomu Takeda, t-takeda@juntendo.ac.jp

Case Rep Gastroenterol 2024;18:386–394
DOI: 10.1159/000540185

Introduction

Among peptic ulcers, those that are *Helicobactor pylori* (HP) negative, not caused by non-steroidal anti-inflammatory drugs (NSAIDs), and whose cause is unknown are called idiopathic peptic ulcers (IPUs) [1]. In recent years, the frequency of conventional HP-positive ulcers has decreased due to improved hygienic conditions and the spread of HP eradication therapy. However, the number of IPUs, which were previously considered rare, has been increasing [2]. In addition, the clinicopathological characteristics of IPUs have not yet been fully elucidated and treatment methods for recurrent and refractory cases remain unestablished.

Potassium competitive acid blockers (PCABs), which suppress gastric acid more strongly than proton pump inhibitors (PPIs), are new gastric acid suppressants. An example is vonoprazan, which is one of the PCABs superior to PPIs in the eradication of first-line HP and erosive esophagitis [1, 3]. Vonoprazan has been used in recent years for the treatment of IPUs. However, the cure rate for IPUs is significantly lower than for HP-associated gastric ulcers after 8 weeks of vonoprazan treatment [4]. Treatment of IPUs may require long-term vonoprazan or another treatment option. Twenty-four-hour intragastric pH monitoring, which has long been used since the era of H2-receptor antagonists (H2-RAs), is useful in the determination of the effectiveness of acid suppressants [5]. Here, we report a case of a refractory IPU that went into remission after the use of 24-h intragastric pH monitoring for a pathophysiological diagnosis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540185).

Case Presentation

In 20XX-6, a man in his forties visited his local doctor after experiencing epigastric discomfort. The patient received 20 mg of rabeprazole but his symptoms did not improve and he was subsequently referred to our hospital. Esophagogastroduodenoscopy (EGD) revealed a H1 stage ulcer in the lesser curvature of the gastric angle. This, in addition to atrophic gastritis (Kimura-Takemoto classification system: C-2 type) of the background mucosa and diffuse redness suggested a HP infection. Treatment consisted of a H2-RA (20 mg of lafutidine) in addition to a PPI. The patient tested positive for HP with a urea breath test (10.9‰) and HP eradication therapy was performed. Primary HP eradication was unsuccessful. Secondary HP eradication therapy was then performed and eradication was subsequently successful (urea breath test; 2.1‰). Since the gastric ulcer still remained 2 months after HP eradication, treatment with 75 mg of polaprezinc, twice a day, was initiated as an additional protective factor. Furthermore, PPI treatment was changed to a PCAB (20 mg vonoprazan, once daily). The gastric ulcer became scarred in 20XX-5 but recurred from 20XX-4 (Fig. 1a–d), and a diagnosis of IPU was made. In 20XX-3, polaprezinc was changed to 100 mg rebamipide, 3 times a day, but the gastric ulcer remained (Fig. 2a, b). In 20XX, the patient was admitted to the outpatient unit due to epigastric discomfort. He had a history of childhood asthma and atopic dermatitis. No special notes were found in the family history. The patient was taking 20 mg of epinastine hydrochloride for allergic rhinitis. His allergy history included reactions to dust mites and house dust. The patient drank three glasses of whiskey with soda and smoked 10 cigarettes daily for more than 20 years. Physical examination revealed that the patient's body mass index was high at 28.3; blood pressure was 108/76 mm Hg; and pulse was 66 beats/min. A blood test revealed iron deficiency anemia with hemoglobin at 12.4 g/dL; the mean corpuscular volume was 68.2 fL; Fe was 36 μg/dL; total iron-binding capacity was

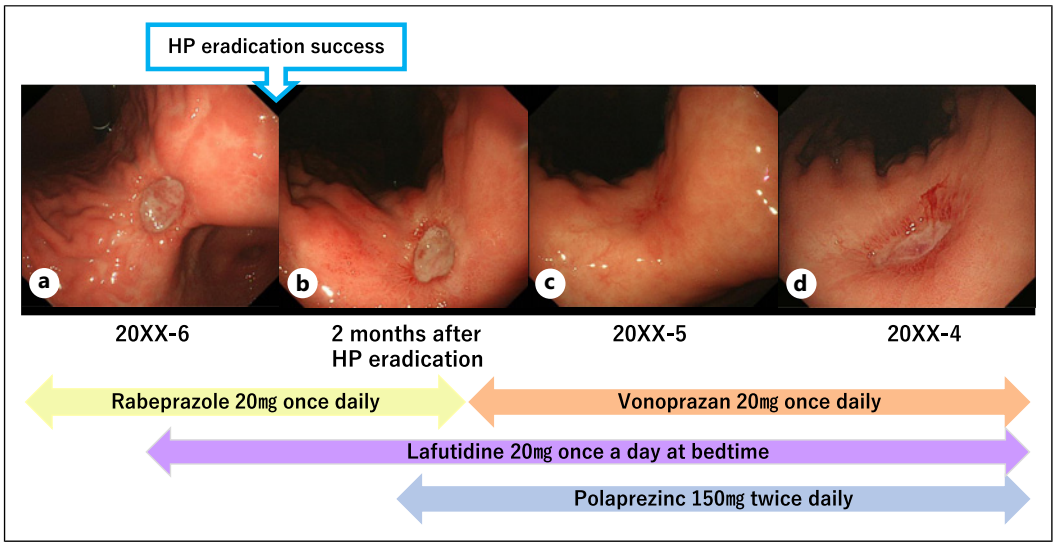

Fig. 1. Clinical course with endoscopic findings in the lesser curvature of the gastric angle between 20XX-6 and 20XX-4. **a** Esophagogastroduodenoscopy revealed a gastric ulcer in the lesser curvature of the gastric angle in 20XX-6. **b** The gastric ulcer still remained 2 months after *Helicobacter pylori* (HP) eradication. **c** The gastric ulcer became scarred in 20XX-5 after the start of vonoprazan treatment. **d** The gastric ulcer recurred in 20XX-4.

476 μg/dL; ferritin was 19 ng/mL; hypertriglyceridemia was 1,384 mg/dL; and hypergastrinemia (gastrin was 807 pg/mL; Table 1). An abdominal computed tomography scan and colonoscopy did not reveal any notable findings. An EGD revealed an ulcer (H1 stage) in the gastric angle (Fig. 2c). A biopsy was taken from the ulcer margin. Histopathological findings showed chronic active inflammation with neutrophilic growth and inflammatory exudates but no malignancy and no bacterial bodies, such as HP or non-HP Helicobacter. Twenty-four-hour intragastric pH monitoring was performed. This showed that the pH was maintained between approximately pH 4 and pH 7 during the day; however, it was about pH 3 from midnight to 4:00 a.m., indicating nocturnal gastric acid breakthrough (Fig. 3a). The patient's medication was changed from H2-RA to prostaglandins (800 μg misoprostol). Additionally for acid suppression at night, the patient's treatment was changed from 20 mg of vonoprazan in the morning to 10 mg of vonoprazan in separate doses, twice daily, in the morning and evening. Subsequently, scarring of the ulcer was observed (Fig. 2d). Twenty-four-hour intragastric pH monitoring conducted in 20XX + 1 showed no improvement in acid suppression (Fig. 3b). With continuing medication, no recurrence of gastric ulcers occurred until 20XX + 4.

Discussion

The frequency of IPUs among gastroduodenal ulcers in Japan is approximately 12–18.2% [4, 6]. These are more common among the elderly [6], with a predilection for the antral region of the stomach and the bulbous region of the duodenum [7]. The recurrence rate of IPUs is 13.9%. In comparison, the recurrence rate of an ulcer with HP is 2.1% [8]. In addition, patients with a history of HP-negative idiopathic bleeding ulcers have a high risk of recurrent ulcer bleeding and mortality [9]; an IPU can be intractable, such as found in this case.

Although the pathogenesis of IPUs is still largely unknown, it has been pointed out that increased acid secretion and hypergastrinemia, increased gastric emptying, genetic

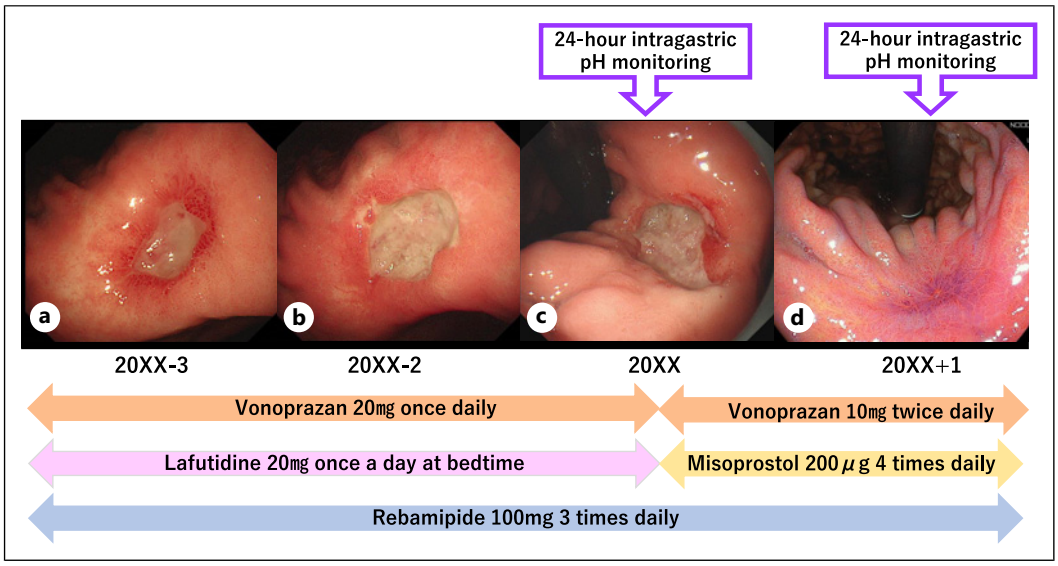

Fig. 2. Clinical course with endoscopic findings in the lesser curvature of the gastric angle between 20XX-3 and 20XX + 1. **a** Esophagogastroduodenoscopy revealed a gastric ulcer in the lesser curvature of the gastric angle in 20XX-3. **b** The gastric ulcer still remained in 20XX-2. **c** The gastric ulcer still remained in 20XX. **d** The gastric ulcer became scarred in 20XX + 1 after the start of misoprostol treatment and changing daily vonoprazan to twice a day (linked color imaging).

predisposition, smoking, weak mucosal defense mechanisms, and psychological stress may be involved [1, 10, 11]. In this case, Crohn's disease, Zollinger-Ellison syndrome, infections such as non-HP *Helicobacter*, cytomegalovirus, and syphilis and eosinophilic gastrointestinal disease were ruled out based on medical history, blood tests, and pathological examinations. Kanno et al. [6] reported that the risk factors for IPUs compared to simple HP-positive ulcers were multiple underlying comorbid diseases (diabetes, hypertension, or hyperlipidemia). The lower region of the stomach and duodenal bulb are highly peristaltic and can be susceptible to the effects of gastric acid secretion and mucosal blood flow if arteriosclerosis exists. Risk factors for this case include a high body mass index, dyslipidemia with high triglyceride levels, and a history of smoking and drinking, which are considered to be a high risk for arteriosclerosis. Arteriosclerosis can cause ischemic changes in the gastric mucosa that can affect the pathology of IPUs. In our case, the patient did not request drug treatment for high triglycerides, and received dietary and lifestyle advice as an outpatient. Triglycerides and alcohol consumption gradually decreased. Accordingly, it is important to continue not only with drug therapy but also dietary and lifestyle guidance in the treatment of IPUs.

No established treatment exists for IPU. The 2020 clinical practice guidelines for peptic ulcer disease in Japan suggest PPIs as first-line treatment for IPUs; PCABs, more potent acid secretion inhibitors than PPIs, may also be effective. Wong reported that among patients with a history of HP-negative idiopathic ulcer bleeding, recurrent bleeding rates in 24 months were 0.88% in the lansoprazole arm and 2.63% in the famotidine arm [12]. Sugawara et al. [4] reported that the healing rate of IPUs using 20 mg vonoprazan was lower than that of simple HP-associated ulcers (81.2 vs. 93.5%). Eight-week vonoprazan treatment may not be sufficient for an IPU, and the longer-term administration or addition of other drugs may be necessary. In this case, vonoprazan was administered for 5 years, but the ulcer recurred. Yamane et al. [13] reported nocturnal acid secretion was measured using 24-h intragastric pH monitoring in a case of an idiopathic gastric antral ulcer. One case showed nocturnal gastric acid breakthrough and, in addition to a PPI, a H2-RA was administered

Case Rep Gastroenterol 2024;18:386–394
DOI: 10.1159/000540185

Table 1. Laboratory data

Hematology	
WBC	7,800/μL
RBC	5.51 × 10^4/μL
Hb	12.4 g/dL
Ht	19.8%
Plt	33.3 × 10^4/μL
Coagulation	
PT	96.0%
APTT	39.6 s
Blood chemistry	
TP	7.5 g/dL
Alb	4.7 g/dL
T-Bil	0.65 g/dL
AST	25 IU/L
ALT	32 IU/L
ALP	154 IU/L
LDH	154 IU/L
γ-GTP	49 IU/L
BUN	15 mg/dL
Cre	0.68 mg/dL
CK	47 U/L
Amy	87 U/L
Na	141 mmol/L
K	4.6 mmol/L
Cl	103 mmol/L
HbA1c	5.2%
Fe	36 μg/dL
TIBC	476 μg/dL
Ferritin	19 ng/mL
TG	1,384 mg/dL
HDL-C	39 mg/dL
LDL-C	108 mg/dL
Serological tests	
CRP	0.1 mg/dL
IgG	894 mg/dL
IgA	109 mg/dL
IgM	123 mg/dL
IgE	664 IU/mL
ANA	20
PR3-ANCA	<1.0 U/mL

Case Rep Gastroenterol 2024;18:386–394
DOI: 10.1159/000540185

Table 1 (continued)

MPO-ANCA	<1.0 U/mL
Gastrin	807 pg/mL
TSH	1.78 μIU/ml
FT3	4.2 pg/mL
FT4	1.6 ng/dL
Tumor marker	
CEA	1.2 ng/dL
CA19-9	6 U/mL
Infection	
HBsAg	(−)
HCVAb	(−)
HIVAg/Ab	(−)
STS	(−)
TPAb	(−)
CMV IgM	0.18
CMV C7HRP	(−)
EBV CA IgM	<10
HSVM IgM	0.22
β-D glucan	<4.0

before sleep; the ulcer eventually became a scar. However, some cases involved ulcers that did not improve even when a H2-RA was added to PPI treatment. We added two types of mucosal protectants and a H2 agonist, but the ulcer did not heal. Twenty-four-hour intragastric pH monitoring revealed nocturnal gastric acid breakthrough. A report described how endoscopically confirmed healing and symptom resolution rates, after twice-daily PPI administration for 8 weeks, were significantly higher than when using once-daily administration in the treatment of refractory reflux esophagitis [14]. We subsequently tried PCAB administration twice a day; the stomach ulcer healed without recurrence for 4 years. Twenty-four-hour intragastric pH monitoring conducted 1 year after the ulcer had healed revealed no improvement in acid suppression. This suggests that PCAB administration twice a day was not successful and that misoprostol likely was effective in this case. The long-term management of IPU has not been established, and maintenance treatment methods will be an issue in future.

We also administered misoprostol, which may have contributed to the healing of the ulcer. Misoprostol is a synthetic prostaglandin E1 analog that replaces the upper gastrointestinal deficiency in prostaglandins caused by NSAIDs [15]. Misoprostol reduces endoscopic ulcers in patients taking NSAIDs [16]. It also improves gastric mucosal blood flow in nicotine- and ethanol-induced gastric injury in rats [17], and may have an effect on gastric mucosal injury in patients with a history of smoking and drinking, as in this case. Although the evidence for misoprostol counteracting peptic ulcers is not high, it can be considered as an option when no improvement occurs with the combination of PPI and other mucosal protective agents. Misoprostol has not been established as a treatment for IPU; PPIs with misoprostol can be recommended for refractory peptic ulcers [18].

The changing epidemiology of HP infection may affect the role of 24-h intragastric pH monitoring. As the number of IPUs increases, the number of refractory IPUs may also

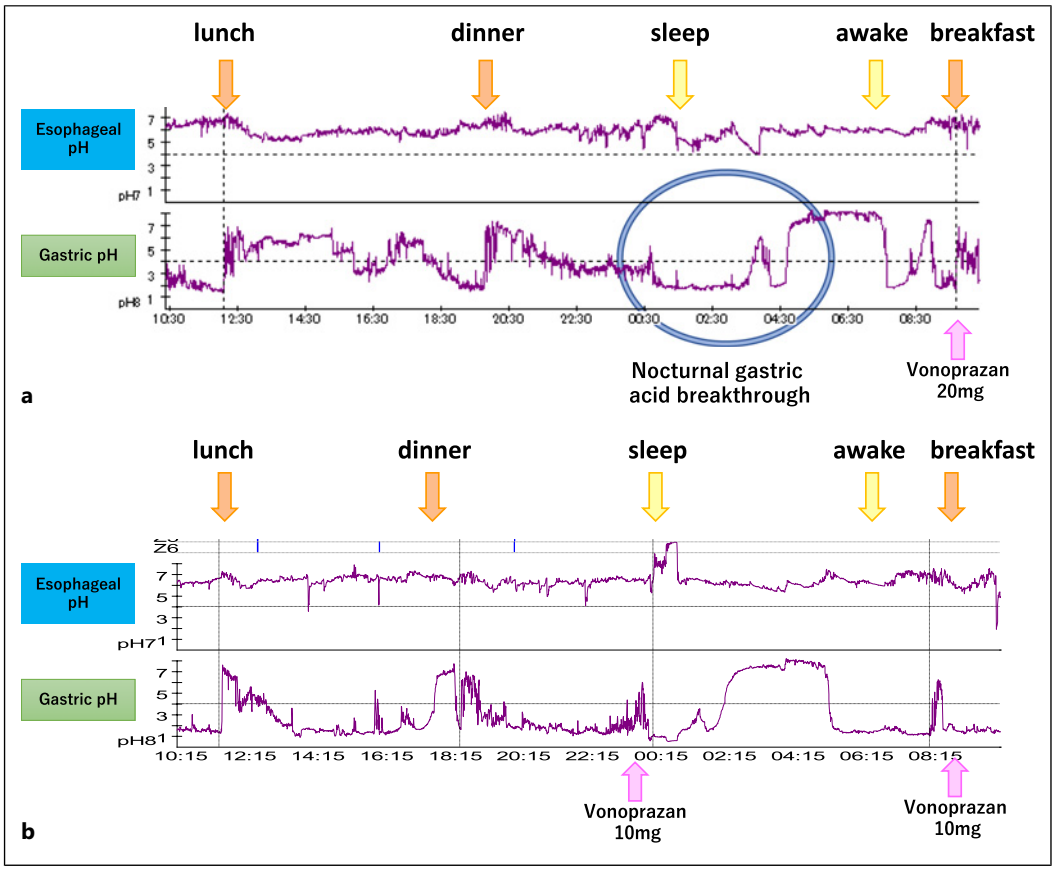

Fig. 3. Twenty-four-hour intragastric pH monitoring. **a** The gastric pH was maintained between approximately pH 4 and pH 7 during the day. However, nocturnal gastric acid breakthrough was observed. **b** The gastric pH 1 year after the ulcer had healed indicated no improvement in acid suppression.

increase. When IPU recurs, 24-h pH monitoring is useful to diagnose the pathophysiology of acid secretion. If the acid suppression effect is insufficient, increasing the dose of PPI or changing to PCAB may be considered. In addition, if acid suppression is insufficient despite using PCAB as in this case, it will also help determine whether to add another agent such as misoprostol.

In conclusion, we describe a case of refractory IPU in which the pathophysiology was assessed using 24-h intragastric pH monitoring and which was treated with PCAB and misoprostol. Twenty-four-hour intragastric pH monitoring provides information on the status of gastric acid secretion that may be useful for diagnosis and treatment. When PPI and PCAB do not improve the IPU, adding a prostaglandin preparation to the treatment may be helpful.

Statement of Ethics

This case report was published in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. Juntendo University Hospital ethics committee approved the study (JHS24-002, April 17, 2024).

Conflict of Interest Statement

The authors declare that they have no conflicts of interest or financial ties relevant to the publication of this paper.

Funding Sources

The authors received no financial support for the research, authorship, or publication of this manuscript.

Author Contributions

Conceptualization: T.T., M.H., and A.N. Study design, T.I., T.T., and A.N. Investigation and data analysis: T.I., T.T., S.O., Y.U., M.Y., R.U., H.U. (Hisanori Utsunomiya), D.A., N.S., A.I., Y.A., K.U., H.U., and M.H. Drafting the manuscript: T.I. and T.T. Writing – reviewing and editing the manuscript: M.H., and A.N. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data obtained in this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding authors.

References

1 Kamada T, Satoh K, Itoh T, Ito M, Iwamoto J, Okimoto T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2020. J Gastroenterol. 2021;56(4):303–22. https://doi.org/10.1007/s00535-021-01769-0
2 Iijima K, Kanno T, Koike T, Shimosegawa T. Helicobacter pylori-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. World J Gastroenterol. 2014;20(3):706–13. https://doi.org/10.3748/wjg.v20.i3.706
3 Iwakiri K, Fujiwara Y, Manabe N, Ihara E, Kuribayashi S, Akiyama J, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. J Gastroenterol. 2022;57(4):267–85. https://doi.org/10.1007/s00535-022-01861-z
4 Sugawara K, Koizumi S, Horikawa Y, Mimori N, Tsuji T, Ishii H, et al. Is the new potent acid-inhibitory drug vonoprazan effective for healing idiopathic peptic ulcers? A multicenter observational study in Akita Prefecture, Japan. J Gastroenterol. 2019;54(11):963–71. https://doi.org/10.1007/s00535-019-01587-5
5 Savarino V, Mela GS, Zentilin P, Scalabrini P, Bonifacino G, Gambaro P, et al. Comparison of the effects of placebo, ranitidine, famotidine and nizatidine on intragastric acidity by means of continuous pH recording. Digestion. 1989;42(1):1–6. https://doi.org/10.1159/000199818
6 Kanno T, Iijima K, Abe Y, Yagi M, Asonuma S, Ohyauchi M, et al. A multicenter prospective study on the prevalence of Helicobacter pylori-negative and nonsteroidal anti-inflammatory drugs-negative idiopathic peptic ulcers in Japan. J Gastroenterol Hepatol. 2015;30(5):842–8. https://doi.org/10.1111/jgh.12876
7 Iijima K, Kanno T, Abe Y, Yagi M, Asonuma S, Ohyauchi M, et al. Preferential location of idiopathic peptic ulcers. Scand J Gastroenterol. 2016;51(7):782–7. https://doi.org/10.3109/00365521.2016.1141316
8 Kanno T, Iijima K, Abe Y, Yagi M, Asonuma S, Ohyauchi M, et al. Helicobacter pylori-negative and non-steroidal anti-inflammatory drugs-negative idiopathic peptic ulcers show refractoriness and high recurrence incidence: multicenter follow-up study of peptic ulcers in Japan. Dig Endosc. 2016;28(5):556–63. https://doi.org/10.1111/den.12635
9 Wong GL, Wong VW, Chan Y, Ching JY, Au K, Hui AJ, et al. High incidence of mortality and recurrent bleeding in patients with Helicobacter pylori-negative idiopathic bleeding ulcers. Gastroenterology. 2009;137(2):525–31. https://doi.org/10.1053/j.gastro.2009.05.006

10 Quan C, Talley NJ. Management of peptic ulcer disease not related to Helicobacter pylori or NSAIDs. Am J Gastroenterol. 2002;97(12):2950–61. https://doi.org/10.1111/j.1572-0241.2002.07068.x
11 Nakajima N, Takeuchi T, Hokari R, Narimatsu K, Iijima K, Koizumi S, et al. Background factors of idiopathic peptic ulcers and optimal treatment methods: a multicenter retrospective Japanese study. J Clin Biochem Nutr. 2024;74(1):82–9. https://doi.org/10.3164/jcbn.23-82
12 Wong GLH, Lau LHS, Ching JYL, Tse YK, Ling RHY, Wong VWS, et al. Prevention of recurrent idiopathic gastroduodenal ulcer bleeding: a double-blind, randomised trial. Gut. 2020;69(4):652–7. https://doi.org/10.1136/gutjnl-2019-318715
13 Yamane T, Ishii T, Umeda A, Shimao H. Evaluation of six cases of idiopathic gastric antral ulcer. Gastroenterol Res. 2012;5(3):120–6. https://doi.org/10.4021/gr437w
14 Kinoshita Y, Hongo M; Japan TWICE Study Group. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. Am J Gastroenterol. 2012;107(4):522–30. https://doi.org/10.1038/ajg.2012.19
15 Kanno T, Moayyedi P. Who needs gastroprotection in 2020? Curr Treat Options Gastroenterol. 2020;18(4):557–73. https://doi.org/10.1007/s11938-020-00316-9
16 Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol. 2018;3(4):231–41. https://doi.org/10.1016/S2468-1253(18)30037-2
17 Hui WM, Chen BW, Cho CH, Lam SK, Luk CT. The effect of misoprostol, omeprazole and sucralfate on nicotine- and ethanol-induced gastric injury and gastric mucosal blood flow: a comparative study. J Gastroenterol Hepatol. 1990;5(6):653–8. https://doi.org/10.1111/j.1440-1746.1990.tb01120.x
18 Borao LC, Lanas A. Advances in the pharmacotherapeutic management of refractory peptic ulcers. Expert Opin Pharmacother. 2023;24(7):825–33. https://doi.org/10.1080/14656566.2023.2199922