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Review

Rescue therapy for refractory *Helicobacter pylori* infection: current status and future concepts

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***Abstract*:** *Helicobacter pylori* infection is an important issue worldwide, and several guidelines have been published for clinicians to achieve successful eradication. However, there are still some patients who remain infected with *H. pylori* after treatment. Clinicians should identify the reasons that caused treatment failure and find strategies to manage them. We have searched and organized the literature and developed methods to overcome factors that contribute to prior treatment failure, such as poor compliance, inadequate intragastric acid suppression, and antibiotic resistance. To improve compliance, telemedicine or smartphone applications might play a role in the modern world by increasing doctor–patient relationships, while concomitant probiotics could be administered to reduce adverse effects and enhance adherence. For better acid suppression, high-potency and high-dose proton-pump inhibitors or potassium-competitive acid blockers have preferable efficacy. To overcome antibiotic resistance, susceptibility tests either by culture or by genotyping are the most commonly used methods and have been suggested for antibiotic selection before rescue therapy, but empirical therapy according to detailed medical history could be an alternative. Eradication with a longer treatment period (14 days) has a better outcome than shorter period (7 or 10 days). Ultimately, clinicians should select antibiotics based on the patient's history of drug allergy, previous antibiotic exposure, local antibiotic resistance, available medications, and cost. In addition, identifying patients with a high risk of cancer and shared decision-making are also essential for those who have experienced eradication failure.

Keywords: *Helicobacter pylori*, refractory, rescue therapy

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Introduction

Helicobacter pylori (*H. pylori*) is a bacterial species that infects the human stomach, causing chronic gastritis, dyspepsia, and peptic ulcer disease. It is also a known strong risk factor for gastric malignancies such as non-cardiac gastric adenocarcinoma and gastric mucosal-associated lymphoid tissue lymphoma (MALToma).[1–3] Although the prevalence of *H. pylori* varies in different areas, screening and treatment are very important, as eradication of this bacterial infection halts inflammation of gastric mucosa while reducing the incidence of recurrent ulcers and gastric cancer, as well as gastric cancer-related mortality.[4,5]

The goal of treatment for eradication of *H. pylori* infection should always be a 100% cure rate since it is also identified as a class I carcinogen by the World Health Organization (WHO).[6] However, the struggle against it has lasted for decades, as there is no single definitive effective treatment owing to the unique acidic environment of the stomach and antibiotic resistances of *H. pylori*. Several guidelines provide clinicians

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with algorithms to choose eradication strategies, and till now, clarithromycin-based triple therapy is one of the most common regimens in first-line eradication therapies, with levofloxacin triple therapy and bismuth quadruple therapy being the most common second-line treatments overall. Unfortunately, the eradication rate of clarithromycin triple therapy has dropped below 80% with rising clarithromycin resistance globally. In recent guidelines, choosing an eradication therapy should be based on local antibiotic resistance and, if available, determined by susceptibility testing. In areas of high (>15%) or unknown clarithromycin resistance, clarithromycin triple therapy is not recommended as an empirical first-line treatment. Bismuth quadruple therapy or non-bismuth quadruple therapy (such as hybrid, reverse hybrid, or concomitant therapy) might be better choices as first-line regimens. Any second-line therapy should be selected based on previous antibiotic exposure.[1,2,7,8] However, approximately 3–10% of patients remain *H. pylori* infected after two or more unsuccessful treatments, who are then defined as having refractory infection, thereby requiring rescue or salvage therapy.[9]

Treatment for refractory *H. pylori* infection is challenging. In this article, we attempt to determine possible causes and optimal approaches. Patients who require ongoing treatment or follow-up will also be discussed.

Possible factors to be overcome for rescue therapy for refractory *H. pylori* infection

Complex interactions between host, microbial, and systemic factors are attributed to eradication failure.[10] Poor compliance, antibiotic resistance, and inadequate acid suppression are the most commonly mentioned issues. Clinicians should continue to attempt to identify possible reasons for previous treatment failure to avoid subsequent treatment failure and achieve successful eradication.

Increase adherence/compliance

If the cause of eradication failure is related to poor compliance and inadequate treatment duration, clinicians should determine the reasons before starting the next round of eradication treatment. Poor compliance might result from complexity of eradication regimens, high pill burden, and adverse effects of medications.[10,11] Good communication between doctors and patients can improve adherence. Therefore, before rescue therapy is initiated, the importance and indications of *H. pylori* eradication therapy need to be fully explained to the patient, including taking medication in a timely fashion and in correct manner. Potential adverse effects and follow-up plans during and after eradication should be outlined while ensuring that patients completely understand, as rescue therapies often involve more complicated regimens.

In the modern era, newer technologies and tools are able to strengthen the doctor–patient relationship, using the likes of phone calls, smart phone applications, community platforms, or communication software to interact with people receiving eradication treatment. These technologies provide timely reminders to ensure that patients do *not* miss their medication, allow patient to update their condition, and provide help when needed. Two recent studies from China showed that the use of short-message reminders and interactive smartphone applications during treatment improved adherence to primary treatment.[12,13] This could be replicated during rescue therapy because the rescue regimens often complicate and confuse patients.

Reducing adverse effects are another way to increase compliance. As gut microbiota draws more and more clinical attention, studies on the efficacy of probiotics are also growing. Adjuvant probiotic administration could reduce gastrointestinal adverse effects, help subjects adhere to treatment, and improve the eradication rate. Some specific strains such as *Lactobacillus* and *Bifidobacterium* have been shown to inhibit *H. pylori* in multiple pathways, but more prognostic data are needed to evaluate the direct effects on refractory *H. pylori* infection. Besides, antibiotics have impact on gut microbiota, changing the diversity and increase certain antibiotic resistance. Probiotics seem to promote faster recovery of gut microbiota after eradication therapy.[2,10,14,15]

Maintain high intragastric pH

The acidic condition of the stomach is associated with pathogenesis of *H. pylori*.[16] Sustained intragastric acid suppression plays an important role in its eradication because it appears most susceptible to antibiotics when the pH is consistently

around 7. Some antibiotics, including amoxicillin, clarithromycin, and metronidazole, have better efficacy and are more stable in higher pH than in low pH conditions (pH < 2).[17]

Proton-pump inhibitors (PPIs) are extensively used acid suppressors in eradication regimens, not just because of their anti-secretory effect, but also their direct anti-*H. pylori* activity. Most guidelines have suggested double-dose PPI to maintain acid suppression in first- and second-line eradication therapy. In high-dose dual therapy, a higher frequency of PPI is needed, up to three or four times daily, to obtain better antimicrobial effects and stability of amoxicillin. In addition, PPIs should be taken when fasting because foods have negative effects on its pharmacokinetics.[18]

PPIs also differ in their potency, duration, and metabolism. Most of the earlier-generation PPIs are metabolized *via* the cytochrome P450 2C19 (CYP2C19), and many trials have revealed that metabolism-enhancing CYP2C19 phenotypes are associated with lower plasma PPI concentrations, thus attributing to higher rates of eradication failure when PPIs mainly metabolized by CYP2C19 (e.g. omeprazole, lansoprazole) are used. Non-Asians possess significantly higher prevalence of metabolism-enhancing CYP2C19 phenotypes,[18,19] and replacement with more potent PPIs (e.g. esomeprazole or rabeprazole) or higher dosing might be useful in those cases.

Another potent acid-suppressor, potassium competitive acid blocker (P-CAB), binds reversibly to K+ ions and blocks the H+, K+ ATPase enzyme, thus inhibiting acid secretion. Vonoprazan is the P-CAB class leader, showing several advantages over traditional PPIs including rapid onset of action and longer duration of acid suppression while its metabolism is not dependent on the CYP2C19 genotype.[20] It has also demonstrated good results in *H. pylori* eradication, where some studies have revealed superior or non-inferior results to PPI-based therapy for first-line and second-line treatment.[21–24]

Vonoprazan-based regimens are also effective in rescue eradication therapy. In one randomized trial of vonoprazan-based treatment comparing PPI-based triple therapy (e.g. PPI–amoxicillin–sitafloxacin) for 7 days for third-line eradication treatment in Japan, vonoprazan-based triple therapy was more effective than PPI-based triple therapy [intention-to-treat (ITT): 75.8% in vonoprazan-based therapy *versus* 53.3% in PPI-based therapy, $p = 0.07$; per-protocol (PP): 83.3% *versus* 57.1%, $p = 0.04$].[25] Another retrospective study also presented an eradication rate of 93% with vonoprazan–amoxicillin–metronidazole therapy in third-line treatment in Japan.[26] One retrospective study conducted in China to investigate vonoprazan–amoxicillin dual therapy in rescue therapy also showed great response (92% eradication rate),[27] while a small single-arm study demonstrated successful eradication (19/19, 100% eradication) in fourth-line treatment with vonoprazan–amoxicillin–rifabutin in Japan.[28] Another perspective study also showed good efficacy and safety of low-dose rifabutin-based triple therapy with vonoprazan and amoxicillin (ITT: 91.2%, PP: 92.7%)[29] (Tables 1 and 2).

However, vonoprazan is not widely available in most western countries. In addition, the clinical data supporting the use of vonoprazan-based therapies are limited to East Asian populations, so it is unclear whether these findings can be generalized to other parts of the world. As a result, vonoprazan-based therapy is currently only a viable option in Asia.

Aside from PPIs and P-CABs, lifestyle modification should also be considered in eradication therapy. Smoking, for example, can increase intragastric acid, impair gastric mucosal protection, increases complications in *H. pylori*-infected patients, and reduce the success rate of *H. pylo*ri eradication.[30,31] Although there is no clear evidence to support the idea that smoking cessation can promote successful eradication in refractory *H. pylori* infection, it is still recommended during eradication therapy. While other factors that increase acid secretion, such as non-steroidal anti-inflammatory drugs (NSAIDs), caffeine, and alcohol consumption, are less relevant to *H. pylori* eradication, they still represent important areas for future research.

Optimization of antibiotic selection and duration

Choosing appropriate antibiotics is an important but challenging clinical decision, especially with the increasing antibiotic resistance after treatment failure.[32] Clinicians must take into account several factors, such as drug allergies, previous antibiotic exposure, available testing tools and

Table 1. Recent studies for vonoprazan in rescue therapies.

	Regimens	Study designs	Eradication rate
Hirata *et al*.[28]	Vonoprazan 20 mg bid, amoxicillin 750 mg bid, rifabutin 150 mg bid for 10 days	Non-controlled study, prospectively	100% (19/19)
		19 patients	
		As fourth-line therapy	
Gao *et al*.[27]	Vonoprazan 20 or 40 mg per day and amoxicillin 3000 mg per day for 14 days	Non-controlled study, retrospectively	92.5% (172/186)
		186 patients	
		As second- or later-line therapy	
Sue *et al*.[25]	Vonoprazan 20 mg bid, amoxicillin 750 mg bid, and sitafloxacin 100 mg bid for 7 days	Randomized controlled trial	ITT: 75.8% (25/33), PP: 83% (25/30)
		33 patients	
		As third-line therapy	
Saito *et al*.[26]	Vonoprazan 20 mg bid, amoxicillin 750 mg bid, and sitafloxacin 100 mg bid for 7 days	Retrospective study	93% (53/57)
		57 patients	
		As third-line therapy	
Inokuchi *et al*.[29]	Vonoprazan 20 mg bid, amoxicillin 500 mg qid, and rifabutin 150 mg qd for 7 days	Non-randomized controlled study, prospectively	ITT: 91.2% (52/57), PP: 92.7% (51/55)
		57 patients	
		As second- or later-line therapy	

ITT, intention to treat; PP, per-protocol; qd, once a day; bid, two times a day; qid, four times a day.

Table 2. Rescue therapy or regimen recommendation for *Helicobacter pylori* in different guidelines.

	ACG clinical guideline 2017	Maastricht VI 2022	Japanese guideline 2019 revise edition	Taiwan consensus 2017	Estimated eradication rate
Susceptibility-guided therapy	V	V	V	V	60–95%
Bismuth quadruple therapy	V	V		V	65.5–83.8%
Levofloxacin-containing therapy	V	V		V	58.3–73.4%
Rifabutin-based therapy	V	V		V	63–89.6%
High-dose dual therapy	V	V	V		71.3–91.3%
Sitafloxacin-based triple therapy			V		54.2–93%
Concomitant therapy[a]	V	V			Limited data

[a]Concomitant therapy are mostly used for first-line therapy. It is used as rescue therapy only in an area of low clarithromycin resistance (<15%) and after failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy.
ACG, American College of Gastroenterology.

available antibiotics, and local prevalence of antibiotic resistance when selecting antibiotics. Ideally, susceptibility testing-guided therapy is recommended before rescue therapy and even before first-line therapy whenever possible to improve eradication rates.[2,33,34] When bacterial susceptibility is demonstrated, the regimen containing PPI, bismuth plus two susceptible antibiotics is not inferior to PPI with three susceptible antibiotics, and both are recommended as rescue therapy.[35] The gold standard for antibiotic susceptibility testing is the culture-based phenotypical method followed by endoscopic biopsy. Nevertheless, successful culture rate varies and may below 80% in patient who have had treatment failure,[34] and the culture of *H. pylori* is time-consuming and expensive. Genotyping is another method that detects gene mutation to predict antibiotic resistance, and *H. pylori* resistance against clarithromycin and levofloxacin by genotyping is reliable, but other antibiotic resistances are not well established.[36] Whole genome or next-generation sequencing might reveal precise prediction of antibiotic resistance.[2] Ultimately, though susceptibility-guided treatment is recommended in rescue therapy, the evidence is limited. If susceptibility testing is not available, utilizing empirical rescue therapy according to previous antibiotic exposure is not inferior to susceptibility-guided therapy.[9,37]

To choose appropriate antibiotics in areas or hospitals without susceptibility testing, it is essential to obtain and understand the local primary and secondary antibiotic resistance of *H. pylori*. Primary resistance refers to antibiotic resistance in patients without a history of eradication treatment, and secondary resistance refers to antibiotic resistance in patients who have experienced eradication failure. A systemic review and meta-analysis showed that primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin were $\geqslant$15% in all WHO regions, except for primary clarithromycin resistance in the Americas [10%; 95% confidence interval (CI), 4–16%] and South-East Asian regions (10%; 95% CI, 5–16%), and primary levofloxacin resistance in the European region (11%; 95% CI, 9–13%). Globally, there was an increasing trend of antibiotic resistance.[38]

In patients after eradication failure twice, the antibiotic resistance to clarithromycin, levofloxacin, and metronidazole is higher, with one study reporting resistance rates above 80%.[32] Therefore, clarithromycin should only be used in rescue therapy for patients who have never been exposed to clarithromycin and live in areas of low clarithromycin resistance($<$15%), or when susceptibility testing has confirmed susceptibility.[1,2] In contrast, *H. pylori* resistance to tetracycline, rifabutin, and amoxicillin is rare in secondary and even tertiary resistance.[38,39] However, tetracycline is seldom used in combination with amoxicillin due to a decrease in the bactericidal activity of amoxicillin, although some studies have shown non-inferior efficacy compared to other regimens.[40] Consequently, amoxicillin, tetracycline, and rifabutin could be repeated in antibiotics combination, while clarithromycin, metronidazole, and fluoroquinolone cannot.

Bismuth quadruple therapy consists of PPI, bismuth salts, and two antibiotics. PPI–bismuth–metronidazole–tetracycline (PBMT) is the most common bismuth-containing regimen and can be used after failure of clarithromycin-containing therapy, non-bismuth quadruple therapy, or fluoroquinolone-containing therapy.[2,41] Bismuth salts also have antimicrobial activities and gastroduodenal mucosal protective effects.[42] In some studies, higher metronidazole dosage (1600–2000 mg per day) is still effective despite *in vitro* metronidazole resistance. Therefore, bismuth quadruple therapy has shown good eradication rates against metronidazole-resistant strains.[11,43–45] Bismuth quadruple therapy with other antibiotics such as amoxicillin–levofloxacin are logical after previous failure of PBMT, and even repeated PBMT might produce certain effects after the failure of second-line PBMT therapy.[46]

Regimens that contain fluoroquinolones, such as levofloxacin or moxifloxacin, have shown effectiveness as third-line therapy in various studies. They are recommended for patients who have not been previously exposed to fluoroquinolones, for example, after clarithromycin-containing therapy and bismuth quadruple therapy.[1,2] However, increasing resistance to fluoroquinolones negatively affects the eradication rates of these regimens, making them less suitable in areas with high levels of resistance. Adding bismuth may enhance the effectiveness of levofloxacin-containing therapy.[47] Another option is sitafloxacin, a fourth-generation fluoroquinolone that is used as standard third-line treatment in Japan (e.g. PPI–amoxicillin–sitafloxacin

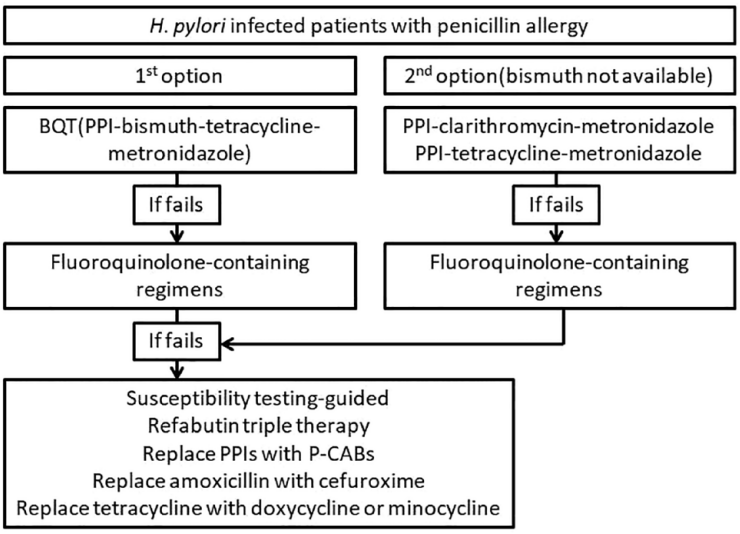

Figure 1. Eradication therapy for *H. pylori*-infected patient with penicillin allergy.
BQT, bismuth quadruple therapy; P-CAB, potassium-competitive acid blockers; PPI, proton pump inhibitor.

or PPI–sitafloxacin–metronidazole). In areas where it is available, replacing the PPI with P-CAB might increase the effectiveness of sitafloxacin-based therapy.[2,26,33]

High-dose dual therapy, such as taking a PPI three or four times a day along with amoxicillin 3000 mg per day in divided doses, can achieve good eradication rates in rescue therapy while causing fewer side effects. However, its efficacy in non-Asian populations may not be as strong as in Asian populations.[48–51] Vonoprazan plus high-dose amoxicillin might be a potential regimen to consider, as it combines a potent acid-suppressive agent with low-resistant antibiotics in a simple treatment that patients are more likely to adhere to.[27]

For patients with multi-drug resistant strains of *H. pylori*, rifabutin-based therapy could be an option, with acceptable eradication rates achieved using regimens such as PPI–metronidazole–rifabutin or PPI–amoxicillin–rifabutin.[52,53] Adding bismuth or switching to vonoprazan as the PPI may enhance the efficacy of rifabutin-based regimens. However, clinicians must also consider the adverse effects of bone marrow suppression and the potential risks of increasing resistance of Mycobacterium.[54,55]

In patients allergic to penicillin (which accounts for approximately 5–10% of patients[56]), *H. pylori* eradication is always a challenge. In such cases, bismuth quadruple therapy is the recommended first-line regimen due to its high eradication rate. Quinolone-based therapy or repeated bismuth quadruple therapy can be used as second-line therapy. However, clinical studies on rescue therapy are lacking, though susceptibility-guided therapy is suggested. Regimens substituting amoxicillin with cefuroxime are reasonable due to the low cross-allergy between penicillin and cefuroxime.[57] Other options to consider include sitafloxacin-based regimens, and those substituting tetracycline with minocycline or doxycycline, as well as rifabutin-based therapy (e.g. PPI–metronidazole–rifabutin)[2] (Figure 1).

It is important to note that treatment duration is also a critical factor. Studies have shown that extending the treatment length of triple therapy to 14 days was superior to using the same regimen for 7 or 10 days in first-line treatment. Therefore, various guidelines recommend a duration of 14 days for first-line treatment,[1,2] and for eradication therapy in general, a longer treatment length of 14 days is recommended.

Does every patient with refractory *H. pylori* infection require rescue therapy?

Most experts recommend rescue therapy for patients with refractory *H. pylori* infection since *H. pylori* eradication is effective in prevention of gastric cancer at any age in adulthood. Long-term PPI is not superior to *H. pylori* eradication in relieving symptoms and recent concerns have been raised about the association between long-term PPI use and infection, chronic kidney disease, and dementia.[2,58] However, some clinicians may view repeating testing and rescue therapy after several treatment failures as less cost-effective, as gastric cancer only develops in 1–3% of *H. pylori*-infected patients. Antibiotic exposure may have long-term effects on gut microbiota, local resistance, and selection of resistant bacteria. Patients may also become fatigued with taking pills and frustrated with the adverse effects of eradication therapies. Nevertheless, if the patient has unexplained anemia or thrombocytopenia, refractory peptic ulcer disease, is on combined antiplatelets/NSAIDs (which increase the risk of peptic ulcer bleeding), is at high risk for cancer (especially those aged over 50, with a positive family history, or with chronic active gastritis before atrophy), or has gastric cancer or

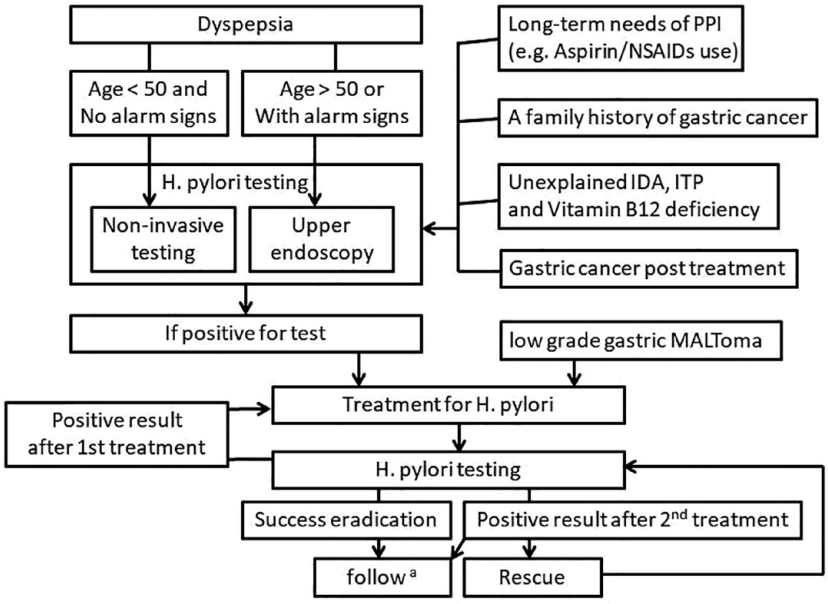

Figure 2. Algorithm for determining which patients require eradication therapy and follow-up for *H. pylori*.
If rescue therapy fails repeatedly and the patient refuses to undergo eradication, but has a high risk of gastric cancer [e.g. family history, severe atrophic gastritis (OGLM III/IV)], it is recommended to closely monitor them with endoscopy.
IDA, iron deficiency anemia; ITP, idiopathic thrombocytopenia purpura; MALToma, mucosal-associated lymphoid tissue lymphoma; PPI, proton pump inhibitor.

MALToma, then efforts should be made to eradicate *H. pylori* to reduce peptic ulcer bleeding and prevent gastric cancer[2] (Figure 2). Clinicians and patients could use shared decision-making to reach a consensus after weighing the *pros and cons* of rescue therapy.

Conclusion

Eradicating *H. pylori* is crucial in reducing the diseases and complications associated with it. Therefore, every effort should be made to eradicate this pathogen, and strategies to avoid treatment failure and increase eradication rates are essential. When faced with a patient requiring rescue therapy for refractory *H. pylori* infection, issues such as patient compliance, maintenance of gastric acid suppression, and antibiotic selection are the most common concerns. However, it is equally important to identify patients who have failed eradication therapy multiple times but are still at high risk and require subsequent treatment. Clinicians should choose the best intervention for their patients based on available resources, including cost-effectiveness, public health policy, and shared decision-making.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Author contribution(s)

Song-Wei Wang: Conceptualization; Writing – original draft.

Fang-Jung Yu: Data curation.

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Chao-Hung Kuo: Conceptualization; Investigation; Writing – review & editing.

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Competing interests
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