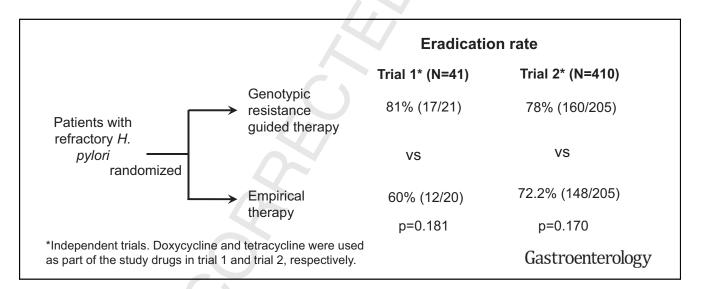
# Efficacies of Genotypic Resistance-Guided vs Empirical Therapy for Refractory *Helicobacter pylori* Infection

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BACKGROUND & AIMS: We aimed to compare the efficacy of genotypic resistance-guided therapy vs empirical therapy for eradication of refractory Helicobacter pylori infection in randomized controlled trials. METHODS: We performed 2 multicenter, open-label trials of patients with H pylori infection (20 years or older) failed by 2 or more previous treatment regimens, from October 2012 through September 2017 in Taiwan. The patients were randomly assigned to groups given genotypic resistance-guided therapy for 14 days (n = 21 in trial 1, n = 205 in trial 2) or empirical therapy according to medication history for 14 days (n = 20 in trial 1, n = 205 in trial 2). Patients received sequential therapy containing esomeprazole and amoxicillin for the first 7 days, followed by esomeprazole and metronidazole, with levofloxacin, clarithromycin, or tetracycline (doxycycline in trial 1, tetracycline in trial 2) for another 7 days (all given twice daily) based on genotype markers of

resistance determined from gastric biopsy specimens (group A) or empirical therapy according to medication history. Resistance-associated mutations in 23S ribosomal RNA or gyrase A were identified by polymerase chain reaction with direct sequencing. Eradication status was determined by <sup>13</sup>C-urea breath test. The primary outcome was eradication rate. RESULTS: H pylori infection was eradicated in 17 of 21 (81%) patients receiving genotype resistance-guided therapy and 12 of 20 (60%) patients receiving empirical therapy (P =.181) in trial 1. This trial was terminated ahead of schedule due to the low rate of eradication in patients given doxycycline sequential therapy (15 of 26 [57.7%]). In trial 2, H pylori infection was eradicated in 160 of 205 (78%) patients receiving genotype resistance-guided therapy and 148 of 205 (72.2%) patients receiving empirical therapy (P = .170), according to intent to treat analysis. The frequencies of adverse effects and

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compliance did not differ significantly between groups. CONCLUSIONS: Properly designed empirical therapy, based on medication history, is an acceptable alternative to genotypic resistance–guided therapy for eradication of refractory *H pylori* infection after consideration of accessibility, cost, and patient preference. ClinicalTrials.gov ID: NCT01725906.

Keywords: 23S rRNA; Gyrase A; Susceptibility Testing; Third-Line.

illions of people are infected with *Helicobacter py-*Blori, the causal agent for gastric cancer and peptic ulcer disease, worldwide. 1-5 In the face of rising prevalence of antibiotic resistance, the demand for rescue therapies is increasing.<sup>6,7</sup> Refractory *H pylori* infection usually refers to patients who fail after 2 or more eradication therapies. Many of them are left untreated because susceptibility testing is not widely available. Whereas the earlier Maastricht Consensus and the ASEAN (Association of Southeast Asian Nations) Consensus recommended the use of susceptibility testing-guided therapy after 2 or more eradication failures, more recent consensus reports recommended the use of empirical therapy according to medication history.<sup>8-11</sup> There are several explanations for the contradictory recommendations. Firstly, randomized controlled trials or even observational studies that compare the efficacy of susceptibility testing-guided therapy vs empirical therapy in the treatment of refractory H pylori infection are lacking. 12 The efficacy of susceptibility testing-guided therapy in the third-line treatment was reported only in some uncontrolled case series. 12-15 Secondly, the successful rate of culture is less than perfect, ranging from 75% to 95%, depending on the number and site of sampling and the quality and experiences of each laboratory. 16 Thirdly, the accuracy of susceptibility test is not 100%.16 Fourthly, culture and susceptibility testing is time-consuming, inconvenient, costly, and usually requires endoscopy. Therefore, the Toronto Consensus and the updated Maastricht V Consensus recommended empirical selection of antibiotics according to prior eradication regimens.<sup>8,10</sup>

Point mutations in 23S ribosomal RNA (rRNA) (A2142G, A2142C, and A2143G) were identified in about 90% of clarithromycin-resistant H pylori strains and correlated with treatment failure. 17-19 Point mutations in gyrase A genes that lead to the alteration of amino acids at position 87, 88, 91, and 97 of gyrase A were identified in 90% of strains with levofloxacin resistance and also correlated with treatment failure. 20,21 These point mutations may be detected using isolated H pylori strains, gastric biopsy specimens, or even fecal samples, without the need for culture. Our pilot study showed that the efficacy of genotypic resistance-guided therapy according to 23S rRNA and gyrase A mutations was 82% in the third-line treatment.<sup>22</sup> However, whether such genotype resistance-guided therapy is superior to empirical therapy according to medication history has not been reported. Therefore, we conducted 2 randomized trials to assess whether genotypic

#### WHAT YOU NEED TO KNOW

#### BACKGROUND AND CONTEXT

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#### **NEW FINDINGS**

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#### LIMITATIONS

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#### IMPACT

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resistance-guided therapy is more effective than empirical therapy in the treatment of refractory *H pylori* infection.

## **Materials and Methods**

## Trial Design and Settings

The 2 multicenter, open-label, parallel, randomized trials were approved by the Institutional Review Board of the 9 participating hospitals in Taiwan (ClinicalTrial.gov ID: NCT01725906). The Declaration of Helsinki regarding human experimentation was followed. The trial consisted of 2 parts. We initially used doxycycline as part of the eradication regimen in trial 1. This trial was terminated ahead of schedule due to the low rate of eradication in patients given doxycycline sequential therapy (15 of 26 [57.7%]). We recruited another 410 patients using tetracycline to replace doxycycline under the same study design in trial 2.

# **Participants**

Patients aged 20 years or older with persistent H pylori infection after at least 2 failed eradication therapies were eligible for enrollment. Patients were excluded if any one of the following criteria was present: (1) children and teenagers aged younger than 20 years; (2) history of gastrectomy; (3) gastric malignancy, including adenocarcinoma and lymphoma; (4) previous allergic reaction to the study drugs (amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, and

Abbreviations used in this paper: CI, confidence interval; CLO test, rapid urease test; <sup>13</sup>C-UBT, <sup>13</sup>C-urea breath test; ITT, intention-to-treat; rRNA, ribosomal RNA; PP, per-protocol.

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