

中文題目：抗藥性基因型之測定在幽門螺旋桿菌抗藥性盛行率監測之應用——一項國內多中心之流行病學調查

英文題目：Determination of genotypic resistance in the surveillance of antimicrobial resistance of *Helicobacter pylori* - A multicenter surveillance program in Taiwan

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**前言 (Background):** The eradication rate of clarithromycin-based triple therapy for *Helicobacter pylori* (*H. pylori*) infection has fallen below 80% in many countries due to the increasing prevalence of clarithromycin resistance. Consensus reports recommend that clarithromycin-based triple therapy should not be used in areas where the prevalence of clarithromycin resistance is greater than 15-20%. The prevalence of antibiotic resistance of *H. pylori* varied in different geographic areas and changes over time worldwide. Therefore, a continual surveillance program for the antimicrobial resistance of *H. pylori* is necessary. However, culture and susceptibility tests used to determine the phenotypic resistance (the minimum inhibitory concentration, MIC) is time consuming, relatively low yield rate (80%), and not widely available. Recently, mutations at 23S ribosomal RNA (23S rRNA) and gyrase A (*gyrA*) have been shown to correlate with phenotypic resistance of clarithromycin and levofloxacin, respectively. Genotypic resistance can be determined using either isolated strains or the gastric biopsy specimen, which takes the advantage of continence without doing culture when gastric biopsy specimen is used. Therefore, we aimed to investigate the prevalence of primary and secondary phenotypic and genotypic resistance of *H. pylori* in Taiwan. We also aimed to analyze risk factors of antimicrobial resistance, including the regional differences, in Taiwan.

**材料及方法 (Materials and Methods):** This multicenter study was conducted in eight medical centers in Taiwan. Patients who underwent endoscopy and *H. pylori* tests during 2007 and 2012 were eligible in this multicenter surveillance program. Demographic data and history of eradication therapies were collected prospectively. The minimum inhibitory concentrations (MICs) of clarithromycin, levofloxacin, metronidazole, amoxicillin, and tetracycline were determined in isolated strains by agar dilution tests in the central laboratory in National Taiwan University Hospital. Genotypic resistance for 23S rRNA and *gyrA* mutations was determined on biopsy specimens and *H. pylori* strains.

**結果 (Results):** The prevalence of primary phenotypic resistance for amoxicillin, clarithromycin, metronidazole, levofloxacin, and tetracycline were 2.4% (34/1398), 12% (170/1241), 25.2% (351/1391), 13.1% (183/1398), and 2.8% (36/1309), respectively. The prevalence of primary

genotypic resistance for clarithromycin (23S rRNA mutation) and levofloxacin (gyrase A mutation) were 10.6% (121/1137) and 9.1% (98/1073), respectively. Mutations in 23S rRNA determined on strains and gastric biopsy specimens correlated well with phenotypic resistance for clarithromycin ( $\kappa = 0.726$  and  $0.334$ ,  $p < 0.001$  and  $< 0.001$ , respectively). Mutations in gyrase A determined on strains and gastric biopsy specimens correlated well with phenotypic resistance for levofloxacin ( $\kappa = 0.616$  and  $0.353$ ,  $p < 0.001$  and  $< 0.001$ , respectively). The primary resistance rates were significantly lower in Eastern Taiwan than in other regions for clarithromycin (4.9% [5/103] vs. 12.6% [165/1308],  $p = 0.02$ ), levofloxacin (3.9% [4/103] vs. 13.8% [179/1295],  $p = 0.004$ ), and metronidazole (15.5% [16/103] vs. 26.0% [335/1288],  $p = 0.019$ ), but not for amoxicillin (1.0% [1/103] vs. 2.5% [33/1295],  $p = 0.317$ ) and tetracycline (1.0% [1/103] vs. 2.9% [35/1206],  $p = 0.250$ ). The primary resistance rate of metronidazole was higher in women than in men (31.6% [231/732] vs. 21.2% [160/754],  $p < 0.001$ ). Primary resistance to two and at least three antibiotics occurred in 5.8% (59/1025) and 1.1% (11/1025) of patients, respectively. History of eradication therapy was associated with increased risk of resistance for amoxicillin (OR 1.82, 95% CI 1.2-2.8), clarithromycin (OR 14.5, 95% CI 9.9-21.4), levofloxacin (OR 2.9, 95% CI 2.2-3.7), and metronidazole (OR 1.8, 95% CI 1.5-2.3).

**結論 (Conclusion):** The prevalence of clarithromycin, levofloxacin, and metronidazole resistance varied in different geographic regions, whereas the prevalence of amoxicillin and tetracycline resistance remained low throughout different geographic regions in Taiwan. Prior eradication therapy for *H. pylori* was associated with increased risk for antimicrobial resistance. The prevalence of phenotypic and genotypic resistance of clarithromycin remain lower than 15-20% which indicates that clarithromycin-based therapy remains the treatment of choice in the first line eradication therapy for *H. pylori* infection in Taiwan.

**Keywords:** *Helicobacter pylori*, resistance, prevalence, phenotypic, genotypic, risk factors