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Alimentary Tract

The relationship between the failure to eradicate *Helicobacter pylori* and previous antibiotics use

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ABSTRACT

Background: The previous use of antibiotics is known to correlate positively with antibiotic resistance; whether this is also the case in the eradication of *Helicobacter pylori* infection is unclear.
Aim: To investigate the relationship between the previous use of antibiotics and the failure of eradication therapy in *H. pylori* infection.
Methods: The relationship between the clinical parameters and the failure of *H. pylori* eradication was analyzed in patients administered standard triple therapy and then assessed for the eradication of *H. pylori* based on a C13-urea breath test.
Results: In a multivariate analysis, failure rates increased significantly in patients with a history of clarithromycin (odds ratio [OR], 4.445) or other macrolides (OR, 2.407) use, who were female (OR, 1.339), or who were older than 60 years of age (OR, 1.326). The eradication failure rate in patients with a history of macrolides use for >2 weeks was significantly higher than if the duration of use was <2 weeks (44.8% vs. 29.3%, $p = 0.047$).
Conclusions: A patient's history of macrolides is a useful predictor of the likelihood of standard triple therapy failure in *H. pylori* eradication. The alternatives such as a bismuth-based quadruple or a levofloxacin-containing therapy should be considered in patients treated with macrolides for >2 weeks.

1. Introduction

Helicobacter pylori is a gram-negative bacterium often found in the stomach, where it causes acute and chronic inflammation leading to metaplasia and, over time, neoplastic transformation [1]. The prevalence of diseases attributed to *H. pylori* has decreased worldwide due to strenuous efforts to treat the infection [2,3]. However, the failure rate of *H. pylori* eradication therapy has been increasing because of antibiotic resistance, poor patient compliance, smoking, and underlying diseases including end-stage renal disease (ESRD), diabetes mellitus, and chronic liver diseases [4–6]. Of these, the most common cause is antibiotic resistance. In a meta-analysis, clarithromycin (CLR) resistance reduced the efficacy of triple therapy by 35–60% [7].

Antibiotic resistance is a worldwide problem and the number of resistant bacterial strains is rapidly increasing. In regions with a high prevalence of antibiotic resistance, the failure rate of the first-line treatment for *H. pylori* infection is likely to be high. Thus, clinicians must be aware of the antibiotic resistance profiles when deciding upon a therapeutic regimen for *H. pylori* eradication. However, the determination of antibiotic resistance is often challenging due to practical problems [8–10]. The development of new and simpler approaches to identifying antibiotic susceptibility will facilitate the selection of an optimal therapeutic regimen for *H. pylori* infections based on an ability to predict the likelihood of treatment failure. The relationship between antibiotic resistance and a history of antibiotics use is well established. However, although the resistance of *H. pylori* to several antibiotics has been the focus of several studies, whether a history of antibiotics use increases the risk of treatment failure in patients with of *H. pylori* infections has not been thoroughly investigated. In this study, we examined whether previous antibiotics use is predictive of the failure of standard triple eradication therapy and thereby indicates the need for alternative therapeutic regimens for *H. pylori* eradication.

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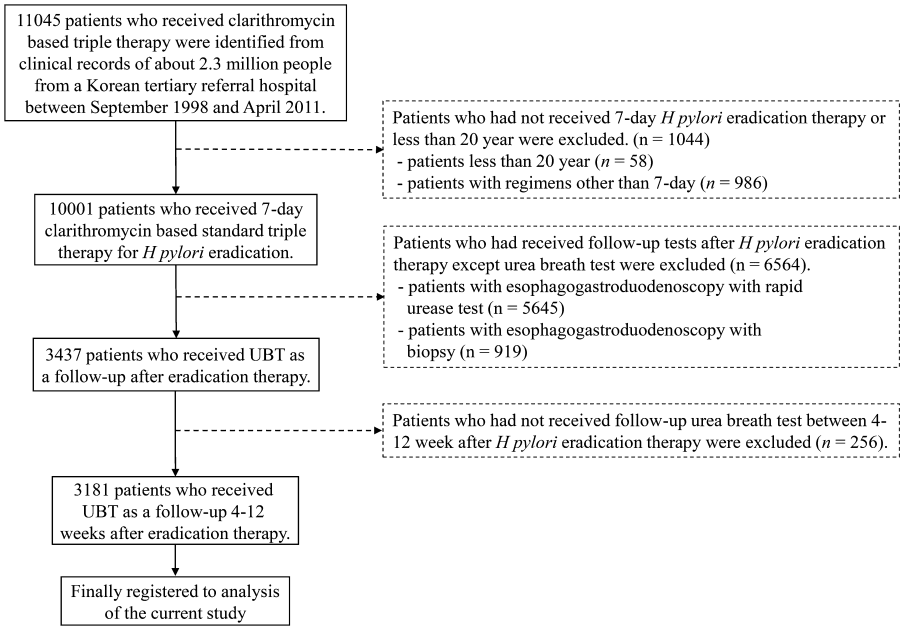

Fig. 1. Study protocol flow sheet. UBT, urea breath test.

2. Materials and methods

2.1. Study population

A retrospective cohort study design was used to identify the previous use of specific antibiotics as a potential risk factor for the failure of *H. pylori* eradication therapy. The data sources used in this study have been reported and described previously [11–15]. The clinical research database consists of clinical, prescriptive, laboratory, and administrative data from the clinical records of the ~2.3 million people seen at a South Korean tertiary teaching hospital (Ajou University Hospital) between June 1994 and June 2012. The database contains records of 105.6 million prescriptions, 141.6 million laboratory tests, and 1.7 million admissions.

The data search and selection process are shown in Fig. 1. All patients ≥20 years of age who, according to the data base, were diagnosed with *H. pylori* infection between August 1998 and May 2011 were included in the study. *H. pylori* infection was diagnosed by esophagogastroduodenoscopy using the rapid urease test and/or biopsy. Patients who had a follow-up urea breath test (UBT) 4–12 weeks after first-line 7-day standard triple therapy consisting of amoxicillin (AMX) 1 g bid, CLR 500 mg bid, and proton pump inhibitors (PPI; lansoprazole, rabeprazole, esomeprazole, or pantoprazole) standard dose bid were included for further study. Only the results of the first-line therapy were used in the analyses of patients who received multiple treatments for *H. pylori* eradication. Exclusion criteria were age <20 years or no follow-up UBT 4–12 weeks after therapy. This study protocol was approved by the Institutional Review Board of Ajou University Hospital. Informed consent was waived because the retrospective data were anonymized.

2.2. Data acquisition

The follow-up UBT results, past use of antibiotics (including AMX, cephalosporins, CLR and all other macrolides, quinolone, tetracycline, metronidazole, and clindamycin) and their length of administration, and underlying diseases of the patients were determined. All antibiotics prescribed before the initiation of *H. pylori* eradication therapy were identified from the inpatient and outpatient records on the basis of their Anatomical Therapeutic Chemical codes. Underlying diseases were identified based on the International Classification of Disease (10th revision) codes and associated tests: diabetes (E10–E11); chronic viral hepatitis with viral markers (hepatitis B virus surface antigen+ or anti-hepatitis C virus+) and abdominal ultrasonography; liver cirrhosis (K74.6) with positive viral markers (hepatitis B virus surface antigen+ or anti-hepatitis C virus+); ESRD (N18.5) or the presence of a registration record for dialysis.

2.3. Main outcome measures

The following determinants were assessed as potential risk factors for the failure of first-line *H. pylori* eradication therapy with PPI-CLR and AMX: previous use of antibiotics (AMX, cephalosporins, CLR, macrolides, quinolone, tetracycline, metronidazole, and clindamycin), age, sex, presence of gastroduodenal ulcer, and chronic underlying disease (diabetes mellitus, chronic hepatitis, liver cirrhosis, laparoscopic cholecystectomy, or ESRD) before therapy.

Additional analyses were performed to determine whether the duration of antibiotic use before *H. pylori* eradication therapy and the interval between eradication therapy and previous antibiotic use were associated with the efficacy of first-line triple therapy for *H. pylori* eradication.

2.4. Statistical analysis

Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the variables according to the characteristics of the patients. The crude risks for the failure to eradicate *H. pylori* were calculated using the *t*-test for continuous variables and the χ^2 test for categorical variables. Determinants identified by univariate analysis as associated significantly with outcome were considered confounding variables and included in the multivariate logistic regression analysis to identify the potential risk factors for the failure of *H. pylori* eradication therapy. A two-tailed *p*-value <0.05 was considered to indicate statistical significance in all analyses. The data were analyzed using MS-SQL 2008 (Microsoft, Redmond, WA, USA) as the database management system and SPSS v. 22.0 for Windows (SPSS, Chicago, IL, USA).