Heteroresistance to clarithromycin and metronidazole in patients with a Helicobacter pylori infection: a systematic review and meta-analysis

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Abstract

Background: Antimicrobial resistance of H. pylori can lead to treatment failure. Importantly, several studies have reported on heteroresistance, i.e. the presence of resistant and susceptible H. pylori populations in the same sample and/or a difference in the susceptibility patterns between biopsy samples. This meta-analysis aims to provide comprehensive data on the prevalence of metronidazole and clarithromycin heteroresistance and the approaches to their detection.

Material and methods: A systematic review was performed after the search of MEDLINE, Scopus and Web of Science. The study outcomes were the weighted pooled prevalence of heteroresistance to clarithromycin and metronidazole in H. pylori positive samples and/or isolates with a subanalysis by continent.

Results: A total of 22 studies that had investigated 3852 H. pylori positive patients were included in the meta-analysis. Heteroresistance to clarithromycin was reported in 20 studies, with a weighted pooled prevalence of 6.8% (95% CI 5.1–8.6; 3654 H. pylori positive patients; the substantial heterogeneity $I^2 = 55.6$%). Heteroresistance to metronidazole was reported in 12 studies, with a weighted pooled prevalence of 13.8% (95% CI 8.9–18.6; 1670 H. pylori positive patients; the substantial heterogeneity $I^2 = 60.9$%). The weighted pooled prevalence of clarithromycin heteroresistance was similar in Asia and Europe (p = 0.174584), however, metronidazole heteroresistance was detected more often in Europe (p < 0.00001). Clarithromycin heteroresistance was detected more often by phenotype rather than by using genotyping methods (12 vs 8 studies), whereas heteroresistance to metronidazole was detected only by phenotype.

Conclusion: The prevalence of heteroresistance to clarithromycin and/or metronidazole is not negligible and can be detected in approximately 7 and 14% of H. pylori positive samples, respectively. These findings highlight the need to raise the awareness of gastroenterologists and microbiologists to the heteroresistance to clarithromycin and metronidazole in patients with a H. pylori infection.

Introduction

Helicobacter pylori, a gram-negative spiral-shaped bacterium, is one of the most prevalent pathogens worldwide [1]. Peptic ulcer disease, or non-ulcer dyspepsia, are the most common clinical conditions of H. pylori...
infection [2]. *H. pylori* is classified as a group 1 carcino-
gen that causes gastric adenocarcinoma [3].

*Helicobacter pylori* eradication treatment decreases
the incidence of duodenal or gastric ulceration and gas-
tic cancer [2]. A combination of proton pump inhibi-
tors, different antimicrobials and/or bismuth are used
for *H. pylori* eradication, however, the increasing anti-
microbial resistance can lead to treatment failure [4].

Antimicrobial susceptibility testing for *H. pylori*
should be performed using the minimal inhibitory con-
centration method as recommended by the European
Committee on Antimicrobial Susceptibility Testing
(EUCAST). However, *H. pylori* is a fastidious organism
that requires specific culture conditions [5]. Moreover,
a delay in the transport of biopsy samples to a labo-
atory, or the use of proton pump inhibitors before
biopsy, can result in a failure to culture *H. pylori* [6]. To
overcome difficulties with *H. pylori* cultures, molecular
assays for the detection of *H. pylori* have been de-
veloped. In addition to pathogen detection, several assays
were designed for the identification of mutations asso-
ciated with clarithromycin and/or levofloxacin [7].

Metronidazole and clarithromycin are included in
non-bismuth quadruple *H. pylori* eradication regimens
(concomitant, sequential and hybrid) and in triple ther-
apy when metronidazole can be replaced by amoxicil-
lin. In addition, metronidazole is a part of the bismuth
quadruple *H. pylori* eradication regimen; [4] resistance
to any of these drugs can lead to treatment failure. The
wide spectrum of mechanisms of metronidazole resist-
ance in *H. pylori* have been described, e.g. genetic rearrange-
ments in the *rdxA* gene (insertions and deletions of
transposons, and missense and frameshift muta-
tions) and point mutations in the *frxA* and *frxB* genes
that can further increase the level of metronidazole
resistance in the presence of mutations in the *rdxA*
gene [8, 9]. The resistance to clarithromycin is caused
by point mutations in the 23S ribosomal subunit (23S
rRNA). Four conserved efflux systems families have
been also described in *H. pylori* strains [10].

In addition to resistance, the occurrence of heter-
oresistance in *H. pylori* isolates or samples has been
reported [11]. Heteroresistance, a mixture of suscep-
tible and resistant patterns, was found in *H. pylori*
isolates and/or samples from the same site of biopsy
(intraniche) or from *H. pylori* isolates and/or samples
from different biopsy sites (interniche) [12]. Interest-
estingly, heteroresistant *H. pylori* causative strains
demonstrate similar fingerprinting patterns [13–17]
suggesting the presence of the same strain with and
without resistance mechanisms (monoclonal hetero-
resistance) rather than a co-infection with different
strains (polyclonal heteroresistance) [11].

This study aims to summarize data on the prevalence of
metronidazole and clarithromycin heteroresistance and
the approaches to their detection.

**Methods**

**Search strategy and study selection**

Three databases including MEDLINE [PubMed], Scopus,
and Web of Science were searched for relevant articles
(Up to February 3rd, 2020) by using the following key-
words: “Helicobacter pylori” OR “H. pylori” AND “het-
erogeneous resistance” OR “resistance heterogeneity” OR
“heteroresistance” OR “antimicrobial heteroresistance”
OR “metronidazole heteroresistance” OR “clarithromycin
heteroresistance” in the Title/Abstract/Keywords fields.
Only studies written in English were included. Reference
lists of all related studies were also reviewed for any other
related publications. The records found by searching the
database were merged and the duplicates were removed
using EndNote X7 (Thomson Reuters, New York, NY,
USA).

**Selection criteria and data extraction**

The information extracted from each study included: (1)
first author; (2) publication year; (3), patient gender and
age (mean, range, paediatrics vs. adults); (4) biopsy site;
(5) number of samples; (6) the method of heteroresis-
tance detection; (7) heteroresistance rates; and (8) a defi-
nition of heteroresistance. A summary of the extracted
data is shown in the Additional file 1: Table S1.

Exclusion criteria were: (1) heteroresistance was not
detected; (2) the results of heteroresistance were not
clearly reported; and (3) data on heteroresistance were
from a meta-analysis and/or systematic review, non-or-
iginal research or conference abstract.

**Statistical analysis**

Studies presenting data on metronidazole and/or
clarithromycin heteroresistance were included in the
meta-analysis which was performed by computing the
pooled prevalence of heteroresistance for each antimi-
crobial agent using a random-effects model [18]. Incon-
sistencies across studies were examined by the forest plot
as well as the I² statistic. Values of I² (25%, 50% and 75%)
were interpreted as the presence of low, medium, or high
heterogeneity, respectively.

**Study outcomes**

The main outcome of the study was the weighted pooled
prevalence of heteroresistance to clarithromycin and
metronidazole with subgroup analysis for the continent
(Asia and Europe).
Results

A total of 3457 records were identified in the initial search. From these, 3432 articles were excluded after an initial screening of the title and abstract due to their irrelevance or duplication. The full texts of the remaining 35 articles were reviewed. From the 35 articles, 13 were excluded for the following reasons: reviews; non-original researches; conference abstract; and non-relevant data or that no heteroresistance data were reported. Finally, 22 studies were included in this systematic review and meta-analysis (Fig. 1, Additional file 1) [12–17, 19–34].

In 22 studies, 3852 *H. pylori* positive patients were investigated. According to the continent, the majority of studies were from Europe (n = 10, 2172 patients), followed by Asia (n = 7, 1331 patients), America (Argentina, Mexico and Colombia 195 patients, Africa (Tunisia, 21 patients) and the Middle East (Turkey and Iran, 133 patients), Table 1, Additional File 1.

Heteroresistance to clarithromycin was reported in 20 studies, with a weighted pooled prevalence of 6.8% (95% CI 5.1–8.6) among 3654 *H. pylori* positive patients; the substantial heterogeneity was $I^2 = 55.6\%$. (Table 1, Fig. 2). Heteroresistance to metronidazole was reported in 12 studies, with a weighted pooled prevalence of 13.8% (95% CI 8.9–18.6) among 1670 *H. pylori* positive patients and substantial heterogeneity ($I^2 = 60.9\%$) (Table 1, Fig. 3).

The weighted pooled prevalence of clarithromycin heteroresistance was similar in Europe (8.4%: 95% CI 3.8–12.9%; $I^2 = 0$), and Asia (5.6%; 2.1–9.1%; $I^2 = 61.8\%$, p-value 0.174584); however, when compared to Asia, the metronidazole heteroresistance was detected more often in European *H. pylori* positive patients (19.6%; 95% CI 5.6–33.6%; $I^2 = 24.7\%$ vs. (7.6%; 95% CI 2.4–12.8%; $I^2 = 73.3\%$), Additional files 2, 3, 4, 5: Fig. S1-S4. Data for the Middle East, Africa and America were not calculated due to the small number of studies.
Clarithromycin heteroresistance was detected by phenotype in 12 studies (agar dilution n = 5, E-test n = 7) and by genotype in eight studies (Table 1). Three studies used the same commercial molecular assay HelicoDR test (Hain Lifescience, Germany). In the study of Navarro-Jarabo et al., this assay was applied to Helicobacter pylori isolates and in the studies of Aguillera-Correa et al. and Güven et al., DNA extracted from biopsy samples was tested [19, 22, 24]. Another commercial assay, BACTfish H. pylori Combi kit (Izinta Kft., Hungary) was used to analyse the biopsy specimens [12]. Two other studies designed their molecular assay: one was based on Real-Time PCR followed by a melting curve analysis using fluorochrome-labelled probes in DNA from H. pylori isolates; the second analysed DNA from gastric brushes samples using droplet digital PCR [20, 21]. In contrast to the heteroresistance to clarithromycin, the heteroresistance to metronidazole was detected only by phenotype (agar dilution n = 4, E-test n = 7, disk diffusion followed by E-test n = 1), (Table 1).

### Discussion

Antimicrobial susceptibility testing is essential for the administration of effective antibiotic treatment and the control of antimicrobial resistance, however, antimicrobial susceptibility testing in causative H. pylori strains is recommended after second-line treatment failure. Given that a combination of antimicrobials is used for the treatment of H. pylori infections, antimicrobial susceptibility testing should be performed to reduce the burden on the patient and decrease the risk of eradication treatment failure through the administration of ineffective antimicrobial drugs [35].

Global data gathered by the World Health Organization (WHO) on the resistance of antimicrobials used for the eradication of H. pylori show an alarming upward trend in all WHO regions [36]. In addition to resistance, the occurrence of heteroresistance in H. pylori isolates or samples has been described [11]. The heteroresistance can be detected intraniche by the presence of susceptible and resistant patterns in one strain and/or sample and interniche when differences in susceptibility patterns are
observed between strains and/or samples from different biopsy sites [12]. As was shown, the interniche heteroresistance can be undetected in one-fifth of cases when only one antrum biopsy site approach is used [12]. Two biopsy sites, where preferably multiple biopsies are taken, can increase the probability of differences in antimicrobial susceptibility patterns [12].

In our meta-analysis that included 22 studies, a weighted pooled prevalence of heteroresistance to clarithromycin was 6.8% (95% CI 5.1–8.6) and heteroresistance to metronidazole was shown to be greater than two times higher at 13.8% (95% CI 8.9–18.6). These data are consistent with the latest WHO data on resistance of *H. pylori* where resistance to metronidazole was found to occur approximately twice as often as resistance to clarithromycin in all WHO regions, except for the Americas [36].

Interestingly, in several studies, the heteroresistant phenotype was detected rarely in several isolates [25], however, other studies have shown an equal or even higher number of heteroresistant samples compared to resistant phenotype [12, 24, 27].

The subgroups analysis of the methods for heteroresistance showed that a majority of studies detected heteroresistance by phenotype; E-test was the most common. Recently, the E-test performance was compared to agar dilution on 72 clinical *H. pylori* isolates and a high essential agreement (>90.0%) was found for amoxicillin, erythromycin, tetracycline and levofloxacin, but it was only 84.7% for metronidazole. However, higher detected rates of resistance by the E-test were not statistically significant [37].

Genotyping methods were used for the detection of mutations in the 23S rRNA gene associated with resistance to clarithromycin [9]. In our meta-analysis, four studies used a commercial molecular assay [12, 19, 22, 24]. Two other studies used lab-developed molecular assays [20, 21]. None of the studies used a genotyping method for the detection of heteroresistance to metronidazole probably due to the nature of the molecular

| Study                        | Prevalence with 95% CI |
|------------------------------|-----------------------|
| Kocsmár et al.               | 0.12 [ 0.08, 0.16 ]   |
| Güven et al.                 | 0.13 [ 0.06, 0.20 ]   |
| Farzi et al.                 | 0.18 [ 0.05, 0.30 ]   |
| Arévalo-Jaimes et al.        | 0.08 [ 0.01, 0.15 ]   |
| Sun et al.                   | 0.27 [ 0.12, 0.41 ]   |
| Mascellino et al.            | 0.10 [ 0.00, 0.20 ]   |
| Navarro-Jarabo et al.        | 0.09 [ 0.06, 0.12 ]   |
| Kao et al.                   | 0.00 [ 0.00, 0.01 ]   |
| Raymond et al.               | 0.11 [ -0.01, 0.23 ]  |
| Lee et al.                   | 0.24 [ 0.03, 0.45 ]   |
| Kim et al.                   | 0.03 [ 0.01, 0.05 ]   |
| Aguilera-Correa et al.       | 0.10 [ 0.04, 0.16 ]   |
| Mansour et al.               | 0.14 [ 0.03, 0.26 ]   |
| Ayala et al.                 | 0.06 [ 0.01, 0.10 ]   |
| Masuda et al.                | 0.17 [ 0.07, 0.27 ]   |
| Rimbara et al.               | 0.05 [ 0.03, 0.06 ]   |
| Norazah et al.               | 0.05 [ -0.04, 0.13 ]  |
| van der Ende et al.          | 0.01 [ 0.00, 0.01 ]   |
| Marzio et al.                | 0.22 [ 0.11, 0.33 ]   |
| Selgrad et al.               | 0.03 [ -0.01, 0.07 ]  |
| **Overall**                  | 0.07 [ 0.05, 0.09 ]   |

![Fig. 2 Clarithromycin resistance in *Helicobacter pylori*-positive samples or isolates](image-url)
mechanisms. The wide spectrum of genetic changes in the rdxA, the main mechanisms of resistance to metronidazole, complicates the design of a molecular assay and, for now, the detection of resistance to metronidazole relies on phenotype-based susceptibility testing [9].

**Conclusion**

The prevalence of heteroresistance to clarithromycin and/or metronidazole is not negligible and can be detected approximately in 7 and 14% of *H. pylori* positive samples, respectively. These findings highlight the need to raise the awareness of gastroenterologists and microbiologists to the heteroresistance to clarithromycin and metronidazole in patients with a *H. pylori* infection. Therefore, data on heteroresistance should be included in a new guidance document for the diagnosis and treatment of *H. pylori* infections [38]. This meta-analysis can serve as solid evidence for this purpose.

**Abbreviations**

EUCAST: European Committee on Antimicrobial Susceptibility Testing; 23S rRNA: 23S ribosomal subunit; WHO: World Health Organization.

**Supplementary Information**

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**Author contributions**

HV, SG, EK, AK, TA, NS: conception and design of the study; the acquisition of data. HS: analysis and interpretation of data. MK: drafting the first version of the manuscript and editing subsequent versions according to the comments of the other authors. All authors read and approved the final manuscript.

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**Declarations**

**Consent for publication**

Informed consent was obtained from all individual participants included in the review.

**Competing interests**

The authors declare that they have no competing interests.

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