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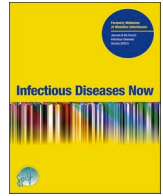
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Short communication

Low-level primary clarithromycin resistance of *Helicobacter pylori* in Reunion Island

Arthur Charazac^{a,b,1}, Raphael Delage^{a,1}, Maxime Pichon^{b,c,*}, Laure Kamus^{a,e}, Benoit Pichard^d, Laura Peyret-Moreau^d, Olivier Belmonte^a, Guillaume Miltgen^{a,e,f}, Christophe Burucoa^{b,c}

^a CHU La Réunion, Microbiology Laboratory, Saint-Denis, La Réunion, France

^b CHU Poitiers, Department of Infectious Agents, Bacteriology Department, Poitiers, France

^c University of Poitiers, U1070 INSERM Pharmacology of Antimicrobial Agents and Antibiotic Resistance, Poitiers, France

^d CHU La Réunion, Département de Gastroenterologie, La Réunion, France

^e University of Reunion Island, UMR Processus infectieux en milieu insulaire tropical (PIMIT), CNRS 9192, INSERM U1187, IRD 249, France

^f Regional Center for Antibiotic Therapy (CRAItb), Saint-Pierre, La Réunion, France

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ABSTRACT

Introduction: The increasing resistance of *Helicobacter pylori* to clarithromycin leads to an ongoing adaptation of empirical first-line treatment for *H. pylori* infections.

Patients and methods: Prospective study (2022–2023) of 364 patients with no previous treatment for *H. pylori* infection, addressed for gastroduodenal endoscopy to the University Hospital of Reunion Island.

Results: PCR tests (Allplex™ *H. pylori* & ClariRAssay, Seegene) performed on gastric biopsy samples detected *H. pylori* DNA in 100 samples (100/364; 27.5 %) and mutations conferring resistance to clarithromycin in 10 of the positive samples (10/100; 10 %). Prevalence of resistance determined by MICs (E-test method) was 41.2 % for metronidazole, 13.2 % for levofloxacin, 8.8 % for clarithromycin. No resistance was detected for tetracycline, rifampicin, and amoxicillin.

Conclusion: The prevalence of primary clarithromycin-resistant *H. pylori* in Reunion Island is below 15 %. Recommendation for the standard clarithromycin-based triple therapy as a first-line treatment can thus be maintained, even though antimicrobial susceptibility testing seems preferable.

1. Introduction

Knowledge of local antibiotic resistance is crucial to choose an effective empirical first-line treatment for *Helicobacter pylori* infections. Clarithromycin is a key component of the standard triple therapy, which is largely used worldwide and more particularly in Reunion Island. However, clarithromycin resistance has been increasing in many countries and constitutes the main risk factor for treatment failure [1]. Clarithromycin resistance is due to point mutations in the 23S ribosomal RNA (rRNA)-coding gene (A2142G, A2143G, and A2142C) [2]. The Maastricht IV to VI consensus reports for management of *H. pylori* infection indicated that the threshold of clarithromycin resistance at which the standard clarithromycin-based triple therapy should not be used, or a clarithromycin susceptibility test should be performed, is

15–20 % [3]. Reunion Island is a French overseas territory harboring 870,000 inhabitants of various origins (Africa, India, Europe, Madagascar, Comoro, Mauritius, Mayotte, China) located in the Indian Ocean. A previous study performed in Reunion Island in 2014 reported clarithromycin resistance prevalence at 12.3 % [4]. The aim of the present study was to evaluate – 10 years later – the prevalence of primary resistance of *H. pylori* not only to clarithromycin, but also to levofloxacin, metronidazole, amoxicillin, tetracycline, and rifampicin in Reunion Island.

2. Patients and methods

A prospective study was performed in 2022–2023 and included 364 patients with no previous treatment for *H. pylori* infection, addressed for

* Corresponding author at: Laboratoire de Bactériologie-Hygiène, BP 577, 86021 Poitiers, France.

E-mail address: maxime.pichon@chu-poitiers.fr (M. Pichon).

¹ Both authors equally contributed to the study.

gastroduodenal endoscopy to the University Hospital of Reunion Island. All patients were informed of the study design and non-opposition to data collecting was obtained. Two gastric biopsies were collected and sent to the laboratory in transport medium at 4 °C (Portagerm Pylori, bioMérieux, Marcy-L'Etoile, France). At reception, biopsies were ground together in 1 ml of saline solution in a BeadBug™ Microtube Homogenizer (Benchmark Scientific, Sayreville, NJ, USA). A total of 300 µL of ground material was used for molecular detection of *H. pylori* and mutations in the 23S rRNA genes that confer resistance to clarithromycin with a real-time PCR kit (Allplex™ *H. pylori* & ClariRAssay, Seegene, South Korea) after DNA extraction with an automated system MicroLab Nimbus™ IVD (Seegene). Culture was performed using 150 µl of ground material on Pylori plates (bioMérieux), as previously described [2]. In case of positive culture of urease-positive and curved Gram-negative bacteria, antimicrobial susceptibility testing was performed according to EUCAST recommendations. MICs were determined using gradient strips on Schaedler plates (Oxoid, Basingstoke, England).

3. Results

A total of 364 patients were included, with a mean age of 55.3 years and a 1.2 sex ratio. The multiplex PCR tests detected *H. pylori* DNA in 100 biopsy samples (n = 100/364; 27.5 %) without identifying any sample with a negative PCR and a positive culture. A very significant difference in infection prevalence according to age groups was observed (p < 0.01): prevalence increased with age to reach 40 % among the age group 66–75, characterizing the well-known cohort effect of *H. pylori* infection. No difference in prevalence was observed according to gender. The prevalence of *H. pylori* infection was significantly higher among people born in Indian Ocean Islands (Reunion, Comoros, Madagascar, Mauritius, and Mayotte Islands) compared to those born in mainland France (n = 94/304, 31 %; and n = 4/51, 7.8 %, respectively; p < 0.01). This finding illustrates the economic and demographic inequalities associated with the origin of birth in this territory, which represent risk factors for *H. pylori* infection. A mutation conferring resistance to clarithromycin was detected in one tenth of the positive samples (n = 10/100; 10 %) with eight harboring an A2143G mutation, one an A2142G mutation, and one a combination of both A2142G and A2142C mutations. No double clarithromycin-susceptible and clarithromycin-resistant mixed populations was observed in the present cohort. The prevalence of primary resistance of clarithromycin-resistant *H. pylori* in this population (10 %) could not be considered statistically different from the prevalence (12.3 %) observed in 2014. With this prevalence (<15 %), healthcare professionals can still follow the standard clarithromycin-based triple therapy recommendation [3]. One should note that the rate of resistance to clarithromycin seems to be higher in subjects born in mainland France than in those born in Reunion Island (25 % and 8.3 %, respectively), without any statistical difference (p > 0.05). This resistance rate is also close to that previously reported in France [5]. Culture and antimicrobial susceptibility testing

(AST) were also performed on the biopsy samples of nearly three quarters of patients (n = 263/364; 72.3 %), leading to the isolation of *H. pylori* in 68 patients (n = 68/263; 25.9 %). Among the 263 patients tested with both culture and PCR test, 77 were positive for PCR and among these patients, 68 were positive for culture (88.3 %). The prevalence of resistance was 41.2 % (n = 28/68) for metronidazole, 13.2 % (n = 9/68) for levofloxacin, and 8.8 % for clarithromycin (n = 6/68). These figures are lower than resistance rates observed in mainland France [5]. To date, no published literature data can help determine the level of resistance in Reunion Island (and in region geographically close to Reunion Island), as well as the mutations involved, in particular resistance to quinolones (and mutations in the QRDR of *gyrA*). No resistance was detected for amoxicillin (n = 0/68; 0 %), rifampicin (n = 0/68; 0 %), and tetracycline (n = 0/68; 0 %).

4. Discussion

In conclusion, a low level of primary clarithromycin resistance (10 %) was reported in our Reunionese patients. The standard clarithromycin-based triple therapy can thus still be recommended as a first-line treatment, even though AST seems preferable.

5. Ethical consideration

The present study was conducted in accordance with the Declaration of Helsinki and national legislation. Due to the retrospective nature of the present study, the need for individual consent specifically for this study was waived, but consent was obtained for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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