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LETTER TO THE EDITOR

Role of high-dose amoxicillin dual therapy for *Helicobacter pylori* eradication in an Irish cohort: A prospective study

Raffaele Palmirotta, Concetta Cafiero, Marica Colella

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Abstract

Helicobacter pylori (*H. pylori*) infections may cause chronic gastritis, peptic ulcer disease, gastric cancers, and other conditions outside of the gastrointestinal tract. Hence, it is important to diagnose and treat it early. *H. pylori* is resistant to certain drugs in traditional eradication therapy, so alternative therapy protocols are needed, such as high-dose amoxicillin dual therapy (HDADT). This article aims to comment on a recent paper by Costigan *et al* in the *World Journal of Clinical Cases*. In this study, the authors recruited 139 patients diagnosed with *H. pylori*, all treated with HDADT. Of these, 93 were treatment-naïve and 46 had received at least one alternative treatment in the past. Four weeks after the end of the treatment, the urea breath test was administered to estimate the eradication rate. The total eradication rate was 56% (78/139), 62% for the treatment-naïve arm and 43% for the previous treatment arm, thus indicating a lower success rate for the arm that had previously received a different treatment regimen. In conclusion, a therapeutic approach with first-line HDADT may potentially be a better treatment, but the results are not sufficient to recommend the use of this regimen in a country with high levels of dual resistance.

Key Words: *Helicobacter pylori*; *Helicobacter pylori* eradication; High dose amoxicillin; High dose amoxicillin dual therapy; Triple therapy

Core Tip: Costigan *et al* conducted a prospective study to test high-dose amoxicillin dual therapy (HDADT) for *Helicobacter pylori* infections in an Irish cohort. Ireland is a high dual-resistance country for clarithromycin and metronidazole, so the traditional treatment does not work well. In addition, bismuth is not available in Ireland; therefore, the only recommended treatment is HDADT. The study considered in this editorial is the first to be conducted in Ireland, and it shows that HDADT does not always guarantee bacterial eradication.

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TO THE EDITOR

Helicobacter pylori (*H. pylori*) is currently recognized as the pathogenic agent of chronic gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and other types of cancers located in the gastrointestinal tract, *i.e.* mucosal associated lymphoid tissue lymphoma[1]. Actually, it is one of the most widespread bacterial infections worldwide[2,3].

In 1994, the World Health Organization recognized *H. pylori* as a class 1 carcinogen[4] and later in 2015, the Kyoto Consensus defined gastritis as an infectious disease, recommending early diagnosis followed by eradication therapy[5]. Over the years some guidelines for this kind of infection were generated. First in 1997, European guidelines suggested triple therapy, which consists of a combination of amoxicillin, proton pump inhibitors (PPIs), and either clarithromycin or metronidazole. However, the use of these antibiotics has allowed the pathogen to develop resistance; indeed, there are some areas considered "high resistance countries", where particularly resistant bacterial strains are present. Therefore, it is necessary to evaluate the right treatment before starting therapy to avoid the risk of failure.

In 2021, the European *H. pylori* Study Group and Consensus Panel released the Maastricht VI/Florence consensus report for the treatment of *H. pylori*. It recommends quadruple therapy (with bismuth or levofloxacin) in high-resistance countries, including Ireland, which has a dual resistance rate of over 15% for both clarithromycin and metronidazole.

In Ireland, bismuth is not available and combination tablets are not an option. In addition, fluoroquinolones are not used because of related adverse reactions[6]. Therefore, it is clear that Ireland requires an efficacious alternative therapeutic approach; for example, a possible second-line or rescue treatment is high-dose amoxicillin dual therapy (HDADT) or rifabutin triple therapy[7]. However, HDADT in naïve patients would be more favorable because it represents a simpler regimen therapy than triple or quadruple therapy. In a recent study, Costigan *et al*[8] sought to determine the effectiveness of HDADT in *H. pylori* infections in an Irish cohort. This editorial aims to comment on their findings.

USE OF HDADT

The study by Costigan *et al*[8] was prospective, open label, and carried out in Ireland in tertiary referral centers. The inclusion criteria were as follows: Patients aged 18 years or older, positive urea breath test (UBT), or positive endoscopy. The exclusion criteria included patients with allergies to penicillin, even if suspected, as well as those who refused to consent or to follow up after eradication.

A total of 187 patients were recruited for the study, of whom 139 were included in the analysis as they met all the inclusion criteria. Out of them, 76 were female (55%) and the mean age was 44.6 years (with a range of 19-83 years).

The 139 patients were divided into two groups: 93 (67%) received HDADT as their first-line therapy, while the other 46 (33%) received an alternative therapy before HDADT. The latter group comprised three subgroups: 32 patients received triple clarithromycin therapy before HDADT, 10 received two prior therapies and four had previously received three or more therapies.

The HDADT treatment is a 14-day course of amoxicillin (1 g three times a day) and esomeprazole (40 mg two times a day). After treatment, the researchers spoke to patients by phone to assess any side effects and to check how well they were complying with the treatment. Four weeks after therapy, the patients had another UBT test to check whether the *H. pylori* had been eradicated. They had to avoid taking PPIs for seven days, antibiotics for 28 days, and food for six hours before the test. The study results show that 78 patients (56%) had complete eradication based on negative post-treatment UBTs. In particular, in the group of patients with prior treatment, 20 out of 46 patients (43%) succeeded in eradicating the pathogen, compared to the first group where 58 patients out of 96 (62%) eradicated it.

Only 10 patients reported side effects, including nausea (10/10), and diarrhea (3/10), and the self-reported compliance was approximately 97%.

The results of the study suggest that first-line treatment seems to have a higher eradication success rate, although it is still below 90%. HDADT also seems to have some advantages in terms of cost and compliance, but its efficacy is too low to be considered first-line therapy. HDADT also appears to have some advantages in terms of cost and compliance, but its efficacy is still too low to be considered first-line therapy.

Unfortunately, this study has some limitations, such as the low number of participants; it is an open-label trial, but it can be considered a pilot study, which is useful for future research. For example, PCR and Epsilometer test (E-test) could be useful to define the pathogen and its resistance to the most used antibiotics, respectively.

Indeed, the management of *H. pylori* infection has undergone significant developments in line with the assessment of antibiotic resistance. This is commonly evaluated through the E-test, a culture-based method that is useful for determining the minimum inhibitory concentration (MIC) of antibiotics. Additionally, molecular techniques such as PCR have been employed to enhance diagnostic accuracy and treatment efficacy[9]. Both methods offer distinctive advantages in identifying infections and antibiotic resistance, which are pivotal for effective management.

A recent retrospective study of 1050 dyspeptic patients diagnosed with *H. pylori* infection showed that antimicrobial susceptibility testing (AST) using the E-test and subsequent tailored antibiotic therapy before first or second treatment had higher eradication rates (83.9% *vs* 73.8%, $P = 0.01$) and (77.3% *vs* 65.6%, $P = 0.27$), respectively, than those without AST[10].

Furthermore, the study demonstrates that the E-test is particularly advantageous in regions characterized by high resistance rates. This enables the implementation of prompt modifications to treatment regimens by susceptibility profiles. Additionally, it facilitates the management of *H. pylori* infection by enabling clinicians to prescribe antibiotic therapy with greater precision, particularly in cases of treatment failure[10].

However, although the E-test is a valuable tool in the management of *H. pylori*, it is essential to remain cautious about its limitations, particularly with regard to metronidazole resistance, for which further confirmation may be required[11].

Molecular methods such as PCR are highly sensitive for detecting *H. pylori* in different types of samples such as gastric juice, gastric biopsies, feces, and saliva. Antibiotic resistance can also be determined by amplification of resistance-associated genes using real-time PCR or by using nucleic acid sequencing methods[12].

In a retrospective study on 192 patients, PCR was correlated to improved eradication rates, with a notable increase in success from 62.2% to 73% after implementing new treatment. The cost-effectiveness of PCR alone was superior compared to culture methods, making it a preferred diagnostic strategy. The study therefore highlighted the cost-effective role of PCR in detecting *H. pylori* and monitoring antibiotic resistance, improving eradication success compared to using the E-test method alone[13].

In a recent study to evaluate the efficacy of real-time PCR assays in identifying *H. pylori* infection and antibiotic resistance in stool samples from 115 patients, the authors demonstrated 99.1% sensitivity and 100% specificity of the method and the ability to effectively assess clarithromycin/Levofloxacin resistance, enhancing tailored eradication treatments without endoscopy and indicating its potential in managing *H. pylori*[14].

Thus, it is evident that PCR and E-testing markedly enhance *H. pylori* management, as evidenced by a study comprising 288 patients with *H. pylori* infection. This study assessed the MIC of six antibiotic classes (metronidazole, clarithromycin, amoxicillin, tetracycline, levofloxacin, and rifampicin) using E-testing. Additionally, the resistance mutations in the rdxA, frxA, 23S rRNA, and gyrA genes of *H. pylori* were evaluated through PCR and targeted gene sequencing. The results therefore indicated that the combined use of these diagnostic methods makes it possible to optimize the selection of first-line and second-line treatment regimens by both preventing the development of resistance and reducing secondary resistance due to treatment failure[15].

On the other hand, the recently published Maastricht VI Consensus recommends routine susceptibility testing (molecular and culture) before prescribing first-line antibiotic treatment[16].

As personalized medicine approaches continue to develop, the pharmacokinetic and pharmacodynamic mechanisms will be better understood. We hope that genotypic analysis will be more accessible so that every patient will be able to take the right and effective dose of the drug, which surely will cause a positive effect[17].

CONCLUSION

Unfortunately, the results of the Costigan *et al*[8] study show that HDADT has limited efficacy as a first-line treatment in an area of high dual resistance. The results are not sufficient to recommend the use of the HDADT regimen in a country with high levels of dual resistance.

Over the last few years, the use of HDADT has increased, particularly in some Middle Eastern countries, to evaluate the efficacy in specific patient groups (*i.e.* children, elderly, *etc.*). This therapeutic choice is for health economic reasons and for the progressive emergence of antibiotic resistance towards the drugs used in triple and quadruple (BCQT) therapy protocols, in particular clarithromycin and metronidazole. On the other hand, these studies allow us to consider HDADT as a first-line treatment in specific populations or in the case of limited economic resources, reserving BCQT as a second-line treatment[18,19].

In 2020, Öztürk *et al*[18] conducted a study on 150 Turkish patients with *H. pylori* infection to test the effectiveness of high-dose dual therapy as a first-line treatment for infection. All patients received a 14-day, high-dose dual therapy comprising rabeprazole (20 mg three times a day) and amoxicillin (1 g three times a day) for *H. pylori* eradication. *H. pylori* stool antigen tests were administered to all participants at least 4 weeks after the completion of the treatment to assess eradication. The high-dose dual therapy demonstrated a 91.3% eradication rate of *H. pylori* infection. Per-protocol success was 94.4% among female patients ($n = 51$) and 89.6% among male patients ($n = 86$); in terms of sex, the differences were not significant ($P = 0.310$). Thus, the authors conclude that high-dose dual therapy with rabeprazole and amoxicillin is highly effective and well tolerated as first-line therapy for *H. pylori* eradication[18].

Similarly, in a more recent randomized controlled trial conducted by Yang *et al*[19] in 2023 on 150 Chinese patients, the authors concluded that 14 days of high-dose dual therapy (pantoprazole 40 mg 3 times daily and amoxicillin 1000 mg 3

times daily for 14 days) had a similar eradication rate as BQT but with fewer side effects, which may be better for elderly patients.

Although HDADT seems to be somewhat effective in these studies, almost all of the studies are inconclusive because the population is very small, and, as mentioned above, no cultural or molecular assessments of antibiotic resistance are included in the protocols. Nevertheless, these studies represent an important basis for future analysis and clinical trials.

FOOTNOTES

Author contributions: Palmirotta R, Cafiero C and Colella M contributed to this paper; Palmirotta R designed the overall concept and outline of the manuscript; Palmirotta R and Colella M contributed to the discussion and design of the manuscript; Palmirotta R, Colella M and Cafiero C contributed to the writing, editing the manuscript, and review of the literature; All authors have read and approved the final manuscript.

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