

PhD THESIS ABSTRACT
**ANTIBIOTIC RESISTANCE OF *HELICOBACTER PYLORI*: IMPLICATIONS IN
OPTIMIZING THERAPEUTIC MANAGEMENT OF INFECTION IN CHILDREN**

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Helicobacter pylori (*H. pylori*) was classified by the WHO as a type 1 carcinogen in 1994 and was included on the priority list for developing new antibiotics in 2017. The infection, often acquired in childhood, can lead to serious complications such as gastritis, peptic ulcer, gastric cancer, or MALT lymphoma. The updated ESPGHAN/NASPGHAN guidelines in 2016 provide recommendations for diagnosing and treating the infection, necessitating that the latter be adapted according to bacterial resistance to antibiotics. In our country, the incidence of paediatric *H. pylori* infection is unknown, and research on antibiotic resistance is limited, particularly in the North-Eastern region of Romania.

General Objectives: This PhD work aimed to determine bacterial resistance to antibiotics (with a focus on clarithromycin - CLR), conduct a comparative assessment of the efficacy of various therapeutic regimens, identify the profile of paediatric patients diagnosed with *H. pylori* infection, and at risk of therapeutic failure, and identify the doctors' approaches regarding the management of paediatric *H. pylori* infection.

The overall methodology involved selecting patients aged 6 to 17 years (inclusive) for inclusion in studies, collecting anamnesis, clinical, and paraclinical data, including endoscopic, histopathological, and PCR investigations of patients, assessing the eradication of the infection, and conducting statistical analysis of the obtained results.

Study 1: The first study was a prospective, analytical, and observational study that included 185 children with digestive symptoms, of whom 116 (62.7%) were diagnosed with *H. pylori* according to ESPGHAN criteria through upper gastrointestinal endoscopy and histopathological examination. The mean age was 13.12 ± 3.27 years, with a predominance of girls (68.10%). Most patients came from rural areas (62.7%), and the prevalence of the infection increased with age, being higher in children over 15 years old. Among the examined group, 61.62% of infected patients had been breastfed for less than six months. Additionally, 47.4% of *H. pylori*-positive patients consumed water from inadequate sources, and 58.4% lived in overcrowded housing. The majority of children (77.5%) had a history of 1-2 respiratory infections per year. The history of antibiotic consumption varied, with most receiving treatments including clarithromycin and amoxicillin. Symptoms that led to the clinical presentation included epigastric pain (62.8%) and recurrent abdominal pain (14.6%). During endoscopic examination, the most common lesions observed were hyperaemia (37.8%) and antral nodularity (20.5%). We used the updated Sydney system for gastritis classification, finding a significant correlation between *H. pylori* infection and the degree of gastric inflammation ($p=0.002$). Adolescent girls in Romania living in rural areas are at high risk of *H. pylori* infection. Epigastric pain and endoscopic antral mucosal nodularity were associated with the infection. As bacterial resistance is unknown in our country, future research is needed to improve eradication rates.

Study 2: This was a randomized controlled prospective study that included 149 patients, of whom 103 were girls (69.12%) and 46 were boys (30.87%), with a mean age of 13.20 ± 3.30 years. The most common symptom leading to upper gastrointestinal endoscopy was epigastric pain (56.37%). The recommended eradication therapy included: proton pump inhibitors (PPIs) + amoxicillin (AMX) + metronidazole (MTZ) for

14 days (41.62%), PPIs + AMX + CLR for 14 days (32.88%), and sequential therapy with PPIs + AMX for 5 days followed by PPIs + CLR + MTZ for another 5 days (25.50%). Compliance at therapy was higher among girls (82.52%) compared to boys (78.26%). Treatment efficacy, assessed through faecal antigen testing, varied: 80.64% for PPIs + AMX + MTZ, 55.11% for PPIs + AMX + CLR, and 63.15% for sequential therapy. Adverse effects were reported by 35.57% of patients, with the most common being the association between nausea and epigastric pain (17.9%). 28 patients stopped the treatment: 22 citing adverse effects and 6 for other reasons. Our country represents an area with unknown *H. pylori* resistance, necessitating the adaptation of therapeutic regimens. Administered as first-line treatment, the triple therapy of PPIs + AMX + MTZ may lead to higher eradication rates.

Study 3: This was a prospective fundamental research study. The investigation included 84 patients with *H. pylori* infection, and the determination of strain resistance to CLR was performed using Real-Time PCR. In the studied cohort, 35 (41.6%) had *H. pylori* strains resistant to CLR, while 49 (58.4%) exhibited sensitive strains. The resistant strains were associated with A2142G/A2143G mutations. Most patients (97.1%) with resistant strains had a history of CLR treatment, which was statistically significant ($p=0.046$). Patients with sensitive strains more frequently presented with epigastric pain, whereas patients with resistant strains experienced recurrent abdominal pain, with significant statistical differences ($p=0.048$). Gastritis assessment according to the Sydney system indicated a higher bacterial density in cases of mild or moderate gastritis ($p=0.045$), without evidence of atrophy or intestinal metaplasia. We identified a significant correlation between mutagenic strains of *H. pylori* and a history of antibiotic therapy, with the presence of wild-type strains significantly correlating with clinical symptoms and endoscopic appearance. The results suggest that the history of antibiotic therapy influences *H. pylori* resistance and the clinical characteristics of patients.

Study 4: This cross-sectional study is based on questionnaires aimed to identify the approaches and knowledge of doctors regarding the indications for testing and eradicating paediatric *H. pylori* infection. The study included 174 responses from physicians across various medical units (private practices, public health facilities, or primary healthcare centres). Of these, 110 responses came from family doctors, 49 from paediatricians, 2 from gastroenterologists, 6 from paediatric gastroenterologists, and 7 from specialists of other fields with paediatric subspecialties. Among study participants, 40 had less than 5 years of clinical experience, 26 between 5 and 10 years, and 108 had over 10 years of experience. The majority of physicians (130) managed paediatric *H. pylori* infection cases. Most respondents indicated that sources of infection transmission are contaminated water and food, and over 95% recommended testing for *H. pylori* in the presence of suggestive digestive symptoms. The preferred diagnostic method was faecal antigen testing, followed by upper gastrointestinal endoscopy. For eradication therapy, the most recommended regimen by 79.2% of respondents was the triple therapy of PPIs, AMX, and CLR. In cases of therapeutic failure, physicians would recommend consulting paediatric gastroenterology and changing the treatment regimen. The most frequently cited causes of failure were lack of adherence to treatment and antimicrobial resistance, with potential consequences of persistent infection primarily including symptom persistence and atrophic gastritis. The results suggest that among the interviewed doctors, there is a high variability in practice and the application of international guidelines remains deficient.

The research findings highlight a high prevalence of *H. pylori* infection, contrary to the declining trend observed globally. Romania, as one of the countries with the highest

incidence of poverty in rural areas among European countries, has specific risk factors such as residence in rural areas, inadequate sanitary conditions in schools and homes, overcrowded housing, and the indiscriminate use of antibiotics, including in the paediatric population. Upper gastrointestinal endoscopy proves to be a valuable diagnostic method, with increased sensitivity and specificity, supported by histological evaluation, which remains useful in the paediatric population. It is imperative to implement strategies to disseminate current guidelines for the diagnosis and eradication of *H. pylori* infection, especially in the context of unknown CLR resistance in Romania. A multidisciplinary approach is essential considering the long-term impact on patient health.