

Burden of *Helicobacter pylori* infection in children undergoing upper gastrointestinal endoscopy in Vietnam

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Helicobacter pylori, first described in 1983, is one of the most common chronic bacterial infections worldwide (1, 2). It is mainly acquired in childhood, persists for life if left untreated, and can cause chronic gastritis, peptic ulcers and, in some cases, contribute to the development of gastric cancer later in adulthood (3–5). Vietnam has a high prevalence of *H. pylori* infection in adults and children (70%) (2). The incidence of peptic ulcer disease in children is on the rise, while the eradication effectiveness is decreasing mainly due to high antibiotic resistance (6–10). The important questions in *H. pylori* research remain what is the true burden of *H. pylori* infection in terms of its prevalence, the incidence of *H. pylori*-associated gastroduodenal complications, its antibiotic resistance patterns, and the effectiveness of treatment in Vietnamese symptomatic children?

In this context, a prospective multicenter clinical series study was conducted at the two tertiary Children's Hospitals in Ho Chi Minh City, Vietnam's largest city to investigate the burden of *H. pylori* infection among Vietnamese children. Between October 2019 and May 2021, a total of 394 children were included with a mean age of 9.4 ± 2.5 years and 217 were girls (55%). Five gastric biopsies were obtained during endoscopy to perform *H. pylori* culture, histological examination, polymerase chain reaction (PCR) to detect urease gene (*ureA*), virulence genes (cytotoxin-associated gene A (*cagA*), vacuolating cytotoxin A (*vacA* genotypes)), and point mutations on 23S rRNA gene conferring clarithromycin resistance. Diagnosis of *H. pylori* infection was based on a positive culture or histological evidence in combination with a positive rapid urease test or a positive PCR assay of *ureA* according to internationally recognized criteria. An eradication treatment was prescribed for patients with confirmed *H. pylori* infection. After completion of therapy, a monoclonal stool antigen test was performed to evaluate the eradication status.

The first result showed a very high prevalence of *H. pylori* infection (80%). In particular, children living in Ho Chi Minh City had a higher prevalence than other neighboring provinces in Southern Vietnam. Level comparable to school-aged children in the community, peptic ulcer

disease was more common than anticipated with a prevalence of 19% while nodularity was the most common endoscopic finding (60.7%) (11). Erosion and erythema accounted for 7.7% and 12.2%, respectively. Of children diagnosed with peptic ulcers, 93.8% were infected with *H. pylori*. Interestingly, among these patients, the *vacA* genotypes *s1/m1* (31.4%) and *s1/m1m2* (indicating mixed infections, 40.4%) were found to be the prevalent strains. Furthermore, *cagA*+ strains were significantly higher in children with ulcers while the *vacA s1/m2* genotype was more common in children without ulcers.

The second result addressed the question of antibiotic resistance. *H. pylori* culture with two separate antimicrobial susceptibility testing was positive in 123 patients. The minimum inhibitory concentrations were determined by the Etest method. A remarkably high primary antibiotic resistance was demonstrated, especially for clarithromycin (68.5%), levofloxacin (55.1%), and metronidazole (31.5%). Notably, amoxicillin resistance reached 25.8%, far exceeding the typical worldwide resistance rate of less than 5% (12). The multidrug resistance accounted for 67.7%. The rate of heteroresistance, the coexistence of susceptible and resistant strains in the same patient, was 6.5%. This is posing significant challenges for treatment since, if only one biopsy is taken in routine, the resistant strains can be missed when only the susceptible strains grow on a plate. Additionally, the prevalence of the A2143G point mutation on the 23S rRNA gene, associated with macrolide resistance, was frequent. However, no other point mutations were detected in Vietnamese children. Interestingly, this is the first report of heteroresistant strains emerging in Vietnamese children.

The third result focused on the accuracy of a monoclonal stool antigen test used to confirm *H. pylori* eradication after treatment in Vietnamese children and for epidemiological purposes. The stool test's sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 87.4%, 95.2%, 99.2%, 51.3%, and 88.4%, respectively. This indicates its useful role in detecting *H. pylori* in epidemiological studies and confirming the eradication post-treatment.

The last result investigated the effectiveness and tolerability of first-line regimens. Among 280 patients prescribed for eradication treatment, the

most commonly used regimen was standard triple therapy containing esomeprazole, amoxicillin, and metronidazole (EAM) (65.4%), followed by quadruple therapy containing esomeprazole, amoxicillin, metronidazole, and bismuth subcitrate (EAMB) (25.7%), and clarithromycin-based triple therapy (EAC) (4.6%). Eradication status was assessed at six weeks after completing the treatment regimens, using a monoclonal stool antigen test. Overall, the success rate was disappointingly low, with only 56.1% (78/139) in the per-protocol analysis and 27.9% (78/280) in the intention-to-treat analysis. The per-protocol eradication rate with EAMB was higher compared to EAM or EAC, but the differences did not reach statistical significance. Surprisingly, the study revealed a higher treatment success rate in boys, but lower rates in underweight children and those infected with *cagA*-positive *H. pylori* strains.

In summary, the findings of this work highlight the problematic prevalence of *H. pylori* infection and peptic ulcer disease in symptomatic children. A complex and high-level antibiotic resistance pattern, including multi-resistance and heteroresistance, necessitates an appropriate management strategy for *H. pylori* infection in Vietnamese children. This includes raising clinician awareness of accurate diagnosis, implementing strict antibiotic stewardship, and optimizing tailored treatment to improve eradication rates and reduce ulcer complications., reinfection, and antibiotic resistance.

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