Impact of Age, Gender, and Addition of Probiotics on Treatment Success for Helicobacter pylori in Children

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Abstract

The primary objective of this study was to evaluate the effect of age, gender, and the use of probiotics with standard treatment regimen on Helicobacter pylori eradication. Based on endoscopic findings and clinical presentation, selected patients were treated with standard triple therapy (omeprazole, clarithromycin, and amoxicillin). Those who failed were offered a repeat treatment with omeprazole, metronidazole, and amoxicillin. After the publications of the possible advantages of probiotic treatment on \textit{H pylori} eradication, the probiotic agent “Probiotica Forte” was routinely added to the treatment. Eradication was noted for 94/130 patients (72\%) and for 128/197 patients (65\%) with or without probiotic agent, respectively (\(P = .23\)). For second-line treatment eradication was noted in 33/46 (72\%) and in 9/20 (45\%) with or without probiotic agent, respectively (\(P = .053\)). The addition of probiotics may improve eradication success especially in addition to second-line treatment.

Keywords

Helicobacter pylori, probiotics, eradication, children, treatment

Introduction

\textit{Helicobacter pylori} is a gram-negative bacterium found on the luminal surface of the gastric epithelium. \textit{H pylori} was first isolated by Warren and Marshall in 1983\textsuperscript{1}. \textit{H pylori} infection is common worldwide, and the prevalence is higher in developing countries and in lower socioeconomic groups\textsuperscript{2,3}. \textit{Helicobacter pylori} infection is acquired early in life (almost always before the age of 10 years), and without proper therapy, it generally persists for life unless specifically treated\textsuperscript{4-9}. In Israel, stool \textit{H pylori} antigen was positive in 30\% of infants at their second year of life\textsuperscript{10}. Early infection is known as a risk factor for development of future complications\textsuperscript{11}.

\textit{Helicobacter pylori} eradication success rates are relatively lacking with regard to gender and young age. While adults are rarely re-infected with \textit{H pylori}\textsuperscript{1,12-14}, 4 studies on children have showed prevalence rates of 2\% to 12.8\% re-infection per patient year\textsuperscript{15}. The mean age of re-infected children was lower than those who were not re-infected, and under the ages of 7 and 5 years, re-infection rates were 66\% and 71\%, respectively\textsuperscript{15}. This has led to the recommendation to postpone treatment beyond this age unless an ulcer or gastric atrophy is present\textsuperscript{16}.

Treatment failure is associated with low compliance, multiple drug treatment regimen, antibiotic resistance, and to re-infection\textsuperscript{17}. Probiotic supplements are probably effective in reducing antibiotic therapy adverse effects. It also prevents \textit{H pylori}-associated complications by reducing its density and preventing gastritis and reduces re-infection rates by inhibition of bacterial adhesion to the gastric mucosa. However, there is a controversy regarding effectiveness of adding probiotics to the triple therapy in order to reduce treatment failure rates\textsuperscript{18}.

The primary objective of this study was to evaluate the effect of age, gender, and the use of probiotics with standard treatment regimen on \textit{H pylori} eradication rate.

Methods

The study was approved by the local ethical committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and

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A total of 409 children (76%) were treated with first-line treatment, and 333 children (81%) had a breath test or stool antigen for assessment of eradication. A total of 121 (36%) and 212 (64%) children were aged 0 to 11 years and 11 to 18 years, respectively. Eradication with first-line treatment was noted in 74/121 (61%) and in 151/212 (71%) children between the ages of 0 and 11 years and between 11 and 18 years, respectively ($P = .068$).

A total of 121 (36%) and 212 (64%) of first-line treated patients were boys and girls, respectively. Successful eradication in boys and girls was 91/121 (75%) and 134/212 (63%), respectively ($P = .028$, odds ratio [OR] = 1.7, confidence interval [CI] = 1.04-2.86). When we examined the role of age, gender, and use of probiotics on eradication success using multivariate logistic regression, we found significant findings only for gender. Odds ratio for successful eradication in boys was 1.7 (CI = 1.04-2.68), $P = .033$. Six children in whom data regarding probiotic supplementation were not mentioned or used other probiotic agents were excluded, leaving 327 children. Eradication was noted for 94/130 patients (72%) and for 128/197 patients (65%) with or without probiotic agent, respectively ($P = .23$). Eighty-six children were treated with second-line therapy. Information regarding probiotic agent addition and eradication verification was available for 66 of them. A total of 46 (70%) and 20 (30%) of them were treated with or without probiotic agent, respectively. Eradication was noted in 33/46 (72%) and in 9/20 (45%) with or without probiotic agent, respectively ($P = .053$).

**Discussion**

Successful treatment of $H$ pylori infection remains a challenge especially in children. Antibiotic resistance, proper treatment adherence, and bacterial factors are all linked to eradication success. With the rising prevalence of antimicrobial resistance, the effectiveness of most commonly recommended treatments has declined to unacceptably low levels ($\leq 80\%$), largely related to development of resistance to clarithromycin. Children are different from adults with respect to $H$ pylori infection on the prevalence of the infection, the complication rate, and a higher rate of antibiotic resistance. This has led to an increasing interest in probiotics as an adjuvant therapy against $H$ pylori. This is stimulated by clinical data showing efficacy of some probiotic strains in $H$ pylori infection, the increasing resistance of pathogenic bacteria to antibiotics, and the proven reduction of antibiotic-associated diarrhea by probiotics.

There is evidence that some strains of *Lactobacillus* and *Bifidobacterium* are able to inhibit $H$ pylori growth through the release of bacteriocins or organic acids, and may also decrease its adhesion to epithelial cells.
addition, probiotics have a possible role in the stabilization of the gastric barrier function and the decrease of mucosal inflammation. Furthermore, probiotics contribute to the healing of the gastric mucosa linked to their antioxidant and anti-inflammatory properties. Several meta-analyses have recently examined the role of probiotics on H pylori eradication success. Lionetti et al reviewed several clinical trials in adults and children, providing conflicting results. In a more recent meta-analysis pediatric study, Li et al included 7 studies consisting of 508 pediatric patients. The pooled ORs of eradication rates by intention-to-treat and per-protocol analysis in the probiotics group versus the control group were 1.96 (95% CI = 1.28-3.02) and 2.25 (95% CI = 1.41-3.57), respectively. They concluded that probiotics supplementation in triple therapy for H pylori infection may have beneficial effects on eradication and therapy-related side effects, particularly diarrhea, in children. Overall, in adults 3 studies reported significantly improved eradication rates, with the remaining 10 showing no improvement. In children, 6 studies showed also conflicting results. They concluded that despite the fact that there is no clear evidence that the addition of probiotics to the eradication therapy increases the eradication rates, it seems to be efficacious for the prevention of antibiotic associated side-effects. We found an advantage for the probiotic agent especially in the second-line treatment. Unlike most previous studies we have used a product containing 5 different strains that may be advantageous.

Data from large pediatric studies on H pylori eradication success rates is relatively lacking for gender and young age group. Since children younger than 5 years of age who are treated and cured of their H pylori infection may be at risk for reinfection, the current recommendations do not recommend treatment unless an ulcer or gastric atrophy is present. This is based on several studies concentrating on reinfection rates. In the article by Magista et al., reinfection was clearly associated with young age. The age of the reinfeected children, at the time of the treatment for the initial infection, was significantly lower than that of non-reinfected children (median age = 7.1 years [range = 2.6-17.4 years] vs 10.9 years [range = 3-17.4 years]; P = .0035). Of the 7 patients younger than 7 years of age, 5 became reinfeected compared with 10 of 45 patients older than 7 years (71% and 22%, respectively; P < .01). Rowland et al previously reported a similar pattern; the mean age of their patients was 5.8 ± 5.6 years in children who became reinfeected and 12.3 ± 3.0 years in those who remained clear of infection (P = .00001). Reinfection occurred rarely in children older than 5 years. Only 2 of 46 children older than 5 years became reinfeected compared with 4 of 6 children younger than 5 years. In their recent study on the risks for H pylori recurrence, Nguyen et al found that young age was the most prominent independent risk factor for H pylori recurrence: adjusted hazard ratio among children aged 3 to 4, 5 to 6, and 7 to 8 years, relative to those aged 9 to 15 years, were, respectively, 14.3 (95% CI = 3.8-53.7), 5.4 (95% CI = 1.8-16.3), and 2.6 (95% CI = 0.7-10.4). The young age risk factor for reinfection was not found in the study by Feydt-Schmidt et al.

Our study results showed a trend for better success rates in older age; nevertheless, this has not reached a statistical significance. Our routine is that children under 7 years are carefully selected for therapy according to severity of symptoms and endoscopic findings and usually after a period of observation without treatment while older children are usually treated based on endoscopic findings and clinical symptoms. This might have influenced toward higher eradication in the younger age group. Interestingly, we found that males had significantly better eradication rate. This has previously noted in a Korean adult study. We could not find similar data for children. The reason is unclear and further studies are recommended.

The main limitation of the study is its retrospective nature. Nevertheless, only one gastroenterologist (RS) was involved with treating the patients, patients received exactly the same treatment regimen with or without probiotics, almost all reported excellent compliance during treatment, and compliance for posttreatment eradication examination (stool antigen or C13 breath test) was relatively good (around 80%).

Conclusion

The addition of probiotics may improve eradication success especially in addition to second-line treatment. Failure rate was higher in females and in younger children. Further prospective studies are mandated to strengthen these findings.

Author Contributions

NW pooled the data, helped with interpretation of the data and writing of the paper. RS designed the study, helped with interpretation of the data and wrote the paper.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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