Will treatment of Helicobacter pylori infection in childhood alter the risk of developing gastric cancer?

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Helicobacter pylori has been classified as a group 1 carcinogen for gastric cancer. It is estimated that there is between a two- and sixfold increase in the risk of developing gastric cancer among infected patients. Among different populations, the risk of H pylori-infected individuals developing gastric cancer varies greatly. However, on a worldwide scale, gastric cancer is the second most common cause of cancer-related death. Therefore, H pylori eradication could help prevent up to three to four million gastric cancer deaths per year.

H pylori is usually acquired in childhood. Because infected children have not harboured the organism for long enough to have developed precancerous lesions, childhood is theoretically an attractive time for H pylori eradication and, thus, could help prevent gastric cancer later in life. However, as H pylori prevalence and the incidence of gastric cancer are falling rapidly in developed nations, widespread population screening programs aimed at the eradication of H pylori in these countries would be enormously expensive. Therefore, except in groups with a high risk for development of gastric cancer (eg, Japanese or those with a strong positive family history of gastric cancer), a population-based test-and-treat policy is not justified.

Key Words: Childhood; Gastric cancer; H pylori; Treatment

THE HELICOBACTER PYLORI/GASTRIC CANCER LINK

In the early 1970s, Haenszel et al (1) reported that gastric cancer appeared to be determined by environmental factors in early life. The recognition of Helicobacter pylori as a gastric pathogen provided an attractive candidate for this previously identified gastric cancer risk factor. Two large seroprevalence studies (2,3) published in 1991 demonstrated a high statistical significance associated between an immune response to H pylori and the occurrence of gastric cancer, thus, giving strong supportive evidence for H pylori as a gastric cancer risk factor. Confirmation of this association came in a prospective study in 2001 (4). In addition, Uemura et al (4) followed 1246 H pylori-positive and 280 H pylori-negative Japanese patients for approximately eight years. In this population, with a known high incidence of gastric cancer, 2.9% of the H pylori-positive and none of the H pylori-negative patients developed gastric cancer during the observation period (4). Koch’s postulates were fulfilled for the relationship between H pylori and gastric cancer in an animal model, with the finding that H pylori-infected Mongolian gerbils developed pyloric adenocarcinoma (5).

IS THE RISK CONTRIBUTED BY H PYLORI TO THE OCCURRENCE OF GASTRIC CANCER MODIFIABLE?

To directly show a benefit of H pylori eradication for the prevention of gastric cancer in most populations would require studies comprising many thousands of patients and decades of follow-up (6). In addition, such studies would pose major ethical dilemmas. The identification of preneoplastic changes in
the gastric mucosa as surrogate markers of gastric cancer could provide end points for such studies that would be reached sooner and, if reversible, would pose fewer ethical difficulties (6).

A widely accepted model of gastric carcinogenesis, originally proposed in the pre-\textit{H pylori} era, suggests that atrophic gastritis and intestinal metaplasia represent intermediate steps in the development of gastric cancer (7). A variety of epidemiological studies (8) have confirmed an association between these preneoplastic changes and the occurrence of gastric cancer, and the presence of \textit{H pylori} infection has been repeatedly linked with atrophic gastritis.

Although these precursor lesions are generally thought to be valid surrogate markers of gastric cancer, studies (6,8,9) of the reversibility of atrophy and intestinal metaplasia by eradication of \textit{H pylori} from the gastric mucosa have yielded conflicting results. In addition, some pathologists think that it is biologically implausible for intestinal metaplasia and advanced gastric atrophy to regress (6). Intestinal metaplasia and atrophy, which includes the stem cell compartment in the gastric neck, probably result from damage and/or somatic or epigenetic changes to the gastric totipotential cells. It is highly likely that this is a 'path of no return' in terms of the ability to reconstitute normal gastric mucosa. Therefore, once intestinal metaplasia and gastric atrophy occur in the gastric mucosa, it may be too late to eradicate \textit{H pylori} to prevent gastric cancer.

**TARGETING \textit{H pylori} IN CHILDHOOD TO PREVENT GASTRIC CANCER**

It is generally accepted that \textit{H pylori} is acquired in childhood (10). Infection rates in adults (at least in developed countries) are low. Because the duration of infection within the pediatric age group is, by definition, shorter than in adults, it appears logical that gastric damage from \textit{H pylori} may be less in children, and the preneoplastic changes of atrophy and intestinal metaplasia may not be present.

A number of recent studies (11-14) have addressed the occurrence of intestinal metaplasia and gastric atrophy in childhood. Although one study (13) of North American children suggested a high prevalence of metaplasia and gastric atrophy among 19 \textit{H pylori}-positive patients, studies of patients from the southern United States and South America (11) and northern (14) and southern (12) Europe suggest that intestinal metaplasia is very rare in children.

At Our Lady's Hospital, Dublin, Ireland, we also failed to find an association between \textit{H pylori} infection in childhood and atrophy/metaplasia. In a study (15) of consecutive upper endoscopies looking at the utility of the Sydney Classification (16) for gastritis in children, we identified 29 children (12%) with \textit{H pylori} infection (15). In the whole cohort, atrophy was present in 5% and intestinal metaplasia was present in one patient. However, no children with atrophy or metaplasia had \textit{H pylori} infection (15).

The absence of evidence for ‘irreversible’ precursor lesions makes children a theoretically attractive group to attempt \textit{H pylori} eradication to prevent gastric cancer. This concept has been strongly supported by a recent prospective study in China by Wong et al (17). In a high-risk region for gastric cancer, 1630 \textit{H pylori}-carrier children who had been randomly assigned to receive \textit{H pylori} eradication or placebo were followed over the follow-up period of seven years, there was no statistical difference in the occurrence of gastric cancer between the treated and nontreated subjects; however, in a subgroup analysis, it was suggested that the prevention of risk for development of gastric cancer in those treated for \textit{H pylori} might have occurred in those without precancerous lesions at the start of the study. Although these results require confirmation (18), they add further support to the idea that children may be an appropriate group in which to eradicate \textit{H pylori} and, thus, achieve maximum risk reduction for the development of gastric cancer.

**IS A POPULATION-BASED TEST-AND-TREAT POLICY JUSTIFIED IN CHILDREN?**

Although the evidence outlined above seems to support the argument for \textit{H pylori} eradication to prevent gastric cancer and, at first glance, points to childhood as the ideal time to undertake eradication, other factors need to be taken into consideration. The falling prevalence of \textit{H pylori} infection worldwide has been mirrored by a rapid decline in gastric cancer, especially in developed countries (19). In the 1930s, gastric cancer was the most common cause of cancer-related death in the United States; however, by the 1980s, it was only the fourth most common and, in 2003, it was calculated to be the eighth most frequent cause of cancer mortality (20). This falling incidence of gastric cancer and \textit{H pylori} prevalence has marked implications for the efficiency and cost benefit of testing and treating \textit{H pylori}. For example, in a sensitivity analysis to evaluate the effect of a test-and-treat policy in a community-based population in western Australia, Forbes and Threlfall (21) concluded (using an intermediate case scenario: 23% reduction in lifetime risk of gastric cancer) that treatment of 617 \textit{H pylori}-positive men or 1639 \textit{H pylori}-positive women would be necessary to prevent one case of gastric cancer. Furthermore, they concluded that if the current annual decline in gastric cancer continues, such a program would be less effective than that which would occur naturally over 15 years.

In a study modelling the cost benefit of screening, Parsonnet et al (22) estimated that eradication of \textit{H pylori} in a group at high risk for gastric cancer could potentially be highly cost-effective (US$4500 per year of life saved for a test-and-treat policy in Japanese Americans). However, screening and treating the general population of a developed country was calculated to be significantly more expensive (US$25,000 per year of life saved). Moreover, that study noted that as the prevalence of \textit{H pylori} decreased, the cost of treating children in the general population would soar (US$869,000 per year of life saved for treating children aged 10 years or less).

**CONCLUSIONS**

In certain groups with a high risk of developing gastric cancer, such as Japanese Americans and possibly those with a strong family history of gastric cancer, population-based \textit{H pylori}-eradication strategies should seriously be considered. However, based on current projections regarding cost-benefit analysis, it would be extremely difficult to justify a general test-and-treat policy for \textit{H pylori} in children to modify the risk of developing gastric cancer later in life.

**ACKNOWLEDGEMENTS:** I am grateful to Marion Rowland for her helpful advice during the preparation of this manuscript and to Jacqueline Ferguson for her secretarial assistance.
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