Should We Screen for *Helicobacter pylori* to Prevent Gastric Cancer?

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Key Words

H. pylori screening • *H. pylori* eradication, economic considerations • *H. pylori* eradication, pros and cons • Gastric cancer, epidemiology • Maastricht III guidelines

Abstract

Although the strategy for *Helicobacter pylori* infection management is well defined and quite well followed in a number of situations, including peptic ulcer disease, the issue of *H. pylori* screening and eradication in the general population still remains. The following debate attempts to find the answer of whether or not *H. pylori* screening should be performed in the asymptomatic population for preventing gastric cancer. As yet, there is no final evidence-based consensus about the need to screen for *H. pylori* in order to decrease the incidence of gastric cancer.

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Epidemiology

Gastric cancer remains the second leading cause of mortality worldwide within the group of malignant diseases after lung cancer and accounts for 10% of cancer-related deaths or 700,000 annual deaths in absolute

figures. Today it is the fourth leading cancer type in incidence (after lung, breast and colorectal cancers), accounting for 8.6% of all cancers. Close to a million new gastric cancer cases are diagnosed annually (934,000 cases as reported by the International Agency for the Research on Cancer (IARC) in 2002) [1, 2].

Gastric cancer is reported to be declining globally, yet only if calculated in ASR figures. But generally the global population is aging and life expectancy is increasing, so considering these factors, more individuals in absolute figures are going to be affected by the disease in absolute figures, and 1.1 million new annual gastric cancer cases will be diagnosed by the year 2010 [2]. Therefore, the problem globally is of increasing importance and is going to increase global healthcare expenditures, continuing to be a major health issue in the coming decades.

Helicobacter pylori has been identified by the WHO as a class I carcinogen, and increases the relative risk for the non-cardia gastric cancer at least sixfold. Different studies have indicated the relative risk increase caused by the bacteria in the range of 4–20, but even the latter could be a substantial underestimate because of the loss of *H. pylori* in the late stages of gastric mucosal atrophy preceding cancer. The prevalence of *H. pylori* infection is declining worldwide, but at the same time in the areas where *H. pylori*-related disease is among the major health problems, the prevalence of the infection is declining very slowly.

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Without an active approach in finding and eradicating *H. pylori* this would take several centuries to prevent gastric cancer in developing countries, while active management might allow to eliminate the disease within a few decades.

Eradication in Symptomatic and/or Middle-Aged Individuals – Is This Not Too Late?

At the moment, *H. pylori* eradication is indicated in symptomatic patients, including patients with atrophic gastritis. The problem with this is that atrophy is not sought for and diagnosed adequately in most of the patients being seen by physicians, not speaking of the asymptomatic population. But not less important is that this might be too late to eradicate *H. pylori* in the situation of an advanced atrophy of the gastric mucosa.

The prospective interventional population-based eradication study from China by Wong et al. [3] with gastric cancer incidence as an endpoint suggests the importance of *H. pylori* eradication prior to the development of pre-malignant conditions. Several cancer cases were diagnosed in patients after the eradication therapy, yet none of these happened in patients without the presence of premalignant lesions at baseline. These results are supported by an experimental work suggesting that only early premalignant lesions are reversible after eradication therapy in a mouse model, while advanced lesions after a prolonged period of infection are not [4]. Since the point of no return has not been determined in humans, there is a significant risk that by eradicating *H. pylori* in the presence of atrophic gastritis or other premalignant lesions, this might be too late to prevent the development of gastric cancer.

What Do the Current Guidelines Say and How Do They Work?

Although not stated directly, the current Maastricht III guidelines [5] already recommend screening for *H. pylori* infection with consecutive eradication of positive cases in the general population. When combining all groups of individuals in whom eradication is indicated, hardly anybody would be left who would not qualify for one of these groups, in particular:

- Peptic ulcer disease is a widespread disease affecting up to 20% of the *H. pylori*-infected individuals (lifetime prevalence) [6].
- In populations with a lower peptic ulcer incidence, functional dyspepsia is a widely prevalent condition; the Kalixandra study demonstrated 37.6% dyspeptic symptoms in a population of Swedish adults at the

time of testing [7], and the lifetime prevalence of dyspepsia would well exceed half of the entire population.

- At any time, about 8% of the population in developed countries are experiencing rheumatic symptoms that are most probably treated with NSAIDs [8], therefore the cumulative consumption of NSAIDs and aspirin would include the major part of such a population.
- Due to the increasing prevalence of gastroesophageal reflux disease (40% symptom prevalence in the adult population according to the results of the Kalixandra study during the period of testing [7]), the proportion of patients receiving long-term proton pump inhibitor treatment is also expected to be quite high.
- In the high-incidence gastric cancer areas of the world, including Eastern Asia, South America and Eastern Europe, families are comparatively large, meaning that the first-degree relatives of gastric cancer patients make up a considerable part of the population in whom eradication is indicated.
- Finally, if there are any patients at all left outside of the previously listed groups and if they are adequately informed about the benefits *H. pylori* eradication could give them, the majority qualifying for such therapy would definitely make the decision favoring eradication.

Considering this, population screening for *H. pylori* and eradication in positive cases is recommended already now. So why does this approach not work in the real life? The problem is the re-uptake of guidelines, which may be too complicated for general practice physicians without a special interest in digestive diseases.

The Maastricht III guidelines were developed to manage *H. pylori*-infected individuals mainly in primary practice. Will this reach the objectives? Research on the success of guideline implementation in primary practice has been performed before. The data obtained by D. Mazza and colleagues indicate that GPs do not in the main follow, or access, the clinical practice guidelines that have been developed. The authors of the study concluded that strategies are required to create a culture for implementing evidence-based guidelines in the general practice, but the process may take 5–10 years to achieve [9]. In developing countries we can expect that this process is going to take a longer time period, but during this period the majority of patients qualifying for *H. pylori* eradication following the Maastricht III guidelines will not receive the treatment, and the incidence of gastric cancer will duly increase over these years.

If the current guidelines indicate *H. pylori* eradication in nearly everybody in the population, but detailed guidelines as they are now will not be followed in general practice, the only solution to achieve the goals stated in the guidelines is to recommend entire population screening for *H. pylori* and eradication of all those found to be positive.

Economic Considerations

There is no doubt that screening for an infection and its management has to be proven from an economical point of view. A number of studies have addressed the issue in respect to *H. pylori*. The modeling based on the UK population and UK costs performed by the Leeds HELP Study Group [10] suggest that population screening for *H. pylori* and treatment would save 1,300 years of life and over GBP 6 million in a target population of 1 million 45-year-olds.

In conclusion, there are a number of reasons to have *H. pylori* sought and eradicated in the general population now, at least in those populations with a high prevalence of infection and a high incidence of gastric cancer.

Cons by Dan L. Dumitrascu

Screening is the method designed to assess a certain variable in a large sample (i.e. asymptomatic population) in order to detect the presence of pathological changes in early stages. Early detection also means a first step towards prevention, thus screening is useful if it represents the starting point of a preventive intervention. The link between gastric cancer and *H. pylori* infection is now largely recognized. Eradication of *H. pylori* is useful in fighting the evolution from inflammation to neoplasia in the gastric mucosa [11, 12].

In an optimistic approach, in order to prevent gastric cancer, we should test everybody for *H. pylori*, then eradicate the bacteria and observe a dramatic decrease in the incidence of gastric cancer [13]. Unfortunately there are some arguments against large-scale screening of *H. pylori* and against the consecutive eradication of *H. pylori* in respect of prophylactic strategies for gastric cancer. These are:

- *H. pylori* is not the single agent involved in the genesis of gastric cancer, thus screening for *H. pylori* would mean fighting against only one (major) enemy and neglecting the others. According to the bio-psycho-social model of diseases [14], genetic and behavioral factors are involved and indeed, antioxidant supplemen-

tation can have similar effects on the risk of gastric cancer in patients at high risk as antibiotherapy [15]. Probably other markers for the identification of individuals at high risk for gastric cancer related to *H. pylori* infection should be identified and used for screening [16].

- Eradication of *H. pylori* may fail frequently, thus screening should become cost-ineffective. Resistance to antibiotics but also to proton pump inhibitors [17] associated with the re-infection with *H. pylori* may make *H. pylori* screening useless. Some time ago the use of antibiotics for orthopedic conditions offered the hope that antibiotherapy could prevent gastric cancer [18], but this report has been a simple illusion.
- Evidence for the efficacy of *H. pylori* eradication for the prevention of gastric cancer is still missing, thus making the population screening ponderous and questionable. Indeed there are only few studies dedicated to this matter. Some are non-randomized, some are randomized. The non-randomized studies found a beneficial effect of *H. pylori* eradication [19–21]. However, the randomized trials offered less enthusiastic results. The well-known paper by Wong et al. [3] showed no difference between subjects submitted to *H. pylori* eradication versus subjects not submitted to eradication. Only a subgroup of subjects without intestinal metaplasia at baseline (thus at lower risk) benefited from the therapy. Two other studies showed similar results [22, 23]. Another study designed in Central Europe simply could not be finished due to poor recruitment [24]. What did not work in Europe worked better in Asia and the study by Zhou et al. [25] showed an advantage for the eradication in respect to the incidence of gastric cancer and atrophic gastritis.

Therefore, like Malfertheiner et al. [26], we consider that at present time the clinical decision to treat a patient is based on established risk profiles. A general screening strategy is necessary and desirable, but we still need stronger evidence and probably a less complex treatment regimen. As long as only patients with a low risk benefit from *H. pylori* eradication [27, 28], it means that the general population should not be screened. We still need cost-efficiency studies. Meanwhile, alternatives like COX-2 inhibitors should be tested for the prevention of gastric cancer [29].

In conclusion, there is no evidence yet to recommend *H. pylori* screening in order to reduce gastric cancer.

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