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# What Is the Best Strategy for Diagnosis and Treatment of *Helicobacter pylori* in the Prevention of Recurrent Peptic Ulcer Bleeding? A Cost-Effectiveness Analysis

Emili Gené, PhD,[1,2,3] Jordi Sanchez-Delgado, MD,[2,3,4] Xavier Calvet, PhD,[2,3,4] Javier P. Gisbert, PhD,[2,5] Rafel Azagra, PhD[6,7]

[1]Servei d'Urgències, Hospital de Sabadell, Corporació Parc Taulí, Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III, Madrid, Spain; [3]Institut Universitari Parc Taulí, Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Unitat de Malalties Digestives, Hospital de Sabadell, Corporació Parc Taulí, Barcelona, Spain; [5]Servicio de Aparato Digestivo, Hospital de la Princesa, Madrid, Spain; [6]Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [7]ABS Badía del Vallés (DAP Cerdanyola), Barcelona, Spain

## ABSTRACT

**Background:** Clinical trials provide evidence of the high effectiveness of *Helicobacter pylori* eradication for preventing recurrent ulcer-related gastrointestinal hemorrhage. The best strategy for curing the infection in this setting is, however, still under debate.
**Objective:** To evaluate four different strategies for prevention of rebleeding in patients with peptic ulcer hemorrhage: 1) test for *H. pylori* and treatment, if positive; 2) proton pump inhibitor maintenance; 3) no preventive treatment; 4) empirical *H. pylori* eradication immediately after bleeding.
**Methods:** A decision analysis model was used, with a time horizon of 2 years and a third-party payer perspective. Costs were estimated for two different settings: a low-cost-for-care area (Spain) and a high-cost area (USA). Main outcome measure was incremental cost-effectiveness ratio for each upper gastrointestinal hemorrhage avoided.
**Results:** Empirical *H. pylori* eradication was the dominant strategy: its estimated rate of recurrent bleeding was lower (6.1%) than those of strategies 1 (7.4%), 2 (11.1%), and 3 (18.4%) and it was the least expensive strategy. The results remained stable when variables were changed inside a wide range of plausible values. Sensitivity analysis also showed that the prevalence of *H. pylori* in bleeding ulcer was the variable that most influenced the results: when it was below 45% in Spain or below 51% in the United States, empirical eradication was not a dominant strategy although it remained cost-effective.
**Conclusion:** In patients with bleeding peptic ulcer, empirical treatment of *H. pylori* infection immediately after feeding is restarted is the most cost-effective strategy for preventing recurrent hemorrhage.
***Keywords:*** bleeding peptic ulcer, cost-effectiveness, *Helicobacter pylori*, prevention, treatment.

## Introduction

Hemorrhage is the most frequent complication of peptic ulcer disease and is associated with substantial morbidity, mortality, and costs [1]. *Helicobacter pylori* eradication is the most efficacious measure for preventing recurrence in infected patients [2]. Current guidelines differ in terms of how and when the *H. pylori* treatment should be performed [3,4]. Some guidelines even encourage empirical eradication therapy [3].

The rationale for empirical eradication is based on three facts. First, the prevalence of *H. pylori* infection in peptic ulcer bleeding is over 90% in our environment [5]. Second, the sensitivity of diagnostic techniques for *H. pylori* infection falls markedly during bleeding [5]. Finally, histology findings are often unavailable at discharge and, in clinical practice studies, more than 50% of bleeding patients were lost to follow-up without receiving treatment [6].

Empirical eradication treatment before discharge is likely to improve compliance. Nevertheless, there are no clinical data to support empirical treatment, and the pharmacoeconomic data are controversial. Sharma et al. [7] reported that testing and treating *H. pylori* was more cost-effective than ulcer healing for preventing recurrent hemorrhage, but their study did not analyze empirical *H. pylori* treatment. Ghoshal et al. [8] found that empirical treatment of *H. pylori* infection was the most cost-effective strategy. The study was, however, restricted to duodenal ulcer patients and did not consider losses to follow-up in the analysis. Finally, Ofman et al. [9] found that the most cost-effective strategy in bleeding patients was to investigate and treat *H. pylori* eradication in those infected, and maintenance with histamine-2 receptor antagonist in noninfected patients. This finding is based, however, on the assumption of 1) a very high prevalence of "idiopathic" ulcers related neither to *H. pylori* nor to nonsteroidal antiinflammatory drugs (NSAIDs) and 2) a very high bleeding relapse rate in this group of "idiopathic" ulcers. These assumptions could not be true as most studies reporting a low prevalence of *H. pylori* infection in bleeding ulcer used only endoscopic tests (usually histology, urease test, or the combination of both) obtained at the moment of the hemorrhage [10], an approach that is known to underestimate the prevalence of the infection [5]. Moreover, studies do not consider losses to follow-up in the analysis [7–9].

Wide geographical differences in costs and in the prevalence of *H. pylori* in bleeding ulcers may also influence cost-effectiveness. For this reason, the present study was designed to provide calculations for two different settings: 1) a setting with a low cost for care and high *H. pylori* prevalence—the Catalonian Public Health Service, and 2) a high-cost-for-care area with (possibly) a low *H. pylori* prevalence—the United States.

The objective of the present study was to compare four different strategies to prevent recurrence in patients with bleeding peptic ulcer: 1) test for *H. pylori* and treatment, if positive; 2) proton pump inhibitor (PPI) maintenance; 3) no preventive treatment as a control branch; and 4) empirical *H. pylori* eradication.

*Address correspondence to*: Emili Gené Tous, Servei d'Urgències, Hospital de Sabadell, Institut Universitari Parc Taulí (UAB), Parc Taulí, s/n 08208 Sabadell, Barcelona, Spain. E-mail: 29833egt@comb.es
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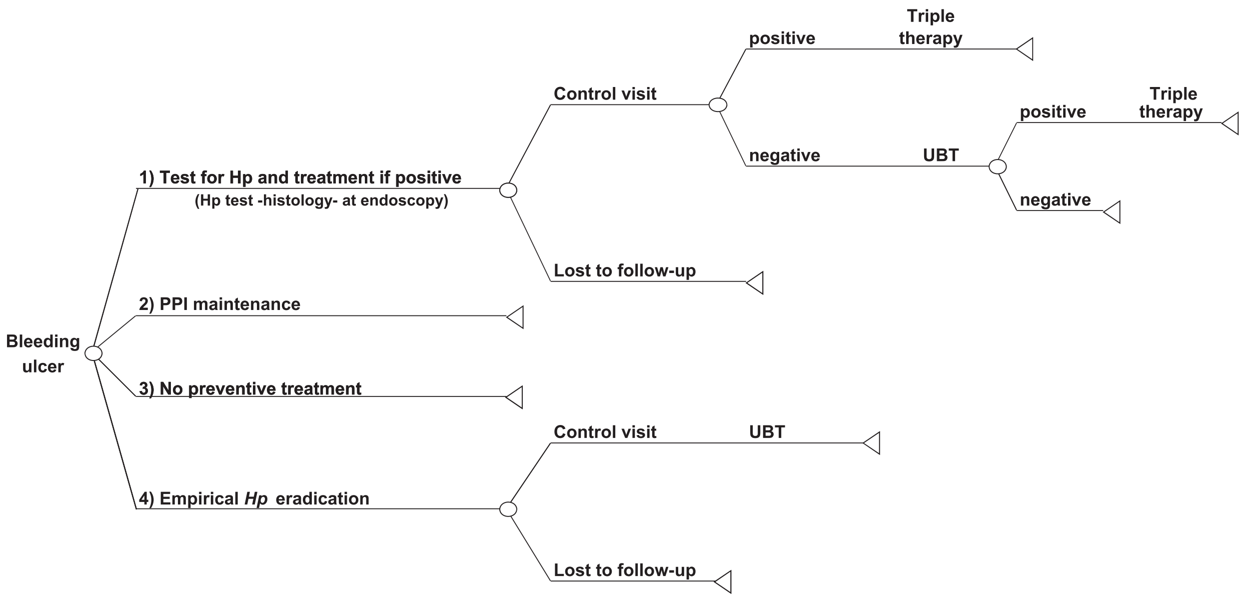


**Figure 1** Decision tree used in the study, identifying decision alternatives. *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor; UBT, urea breath test.

## Material and Methods

A decision analytic model was used. A detailed description of methodology can be found online at the ISPOR Web site.

### Patient Population

The population of the study included patients hospitalized with hemorrhage due to peptic ulcer disease.

### Perspectives and Time Horizon

The perspective was those of a third-party payer—the National Health Service in the case of Catalonia (Spain), and a health insurer in the case of the United States. The time horizon was 2 years.

### Decision Model

Analysis was performed by using a decision tree (Fig. 1). Four initial strategies were analyzed: 1) test for *H. pylori* and treatment, if positive; 2) PPI maintenance; 3) no preventive treatment; and 4) empirical *H. pylori* eradication. NSAID cotherapy and losses to follow-up were considered in all strategies. In the four strategies, patients underwent emergency endoscopy.

In the first strategy, which is currently in use in most centers, *H. pylori* infection was investigated by histology. After resolution of the bleeding, patients were attended on an outpatient basis. A negative initial histology result was interpreted as a probable false negative [5] and was followed by a $^{13}$C-urea breath test (UBT). If subsequent UBT were negative, maintenance PPI therapy was indicated. Patients with a positive *H. pylori* histology or UBT were prescribed triple therapy. Diagnosis of *H. pylori* after treatment was performed with a UBT except for gastric ulcers in which endoscopy and histology were performed to rule out malignancy. Treatment failures received quadruple rescue therapy. In patients in whom a second *H. pylori* treatment was unsuccessful, maintenance PPI treatment was administered.

In strategies 2 and 3, healing therapy with PPI once daily for 8 weeks was prescribed. After this, only patients with gastric ulcer underwent endoscopy. No testing for *H. pylori* or eradication treatment was performed. In the PPI maintenance strategy, all patients were prescribed long-term maintenance PPI. In the "no preventive treatment" strategy, patients did not receive further treatment.

Finally, in the "empirical *H. pylori eradication*" strategy, no test for *H. pylori* was performed after initial endoscopy. Triple therapy was initiated before discharge, as soon as the patient tolerated oral intake. Subsequent follow-up was similar to those of the test-and-treat strategy.

Attempts to discontinue NSAID therapy and long-term PPI prophylaxis in patients requiring continued anti-inflammatory drugs were performed in all strategies.

### Probabilities and Costs

Probability values and ranges used in the sensitivity analysis were taken from the medical literature. For the low-cost area, we obtained cost data mainly from the Catalonian Public Health Service [11]. Costs were expressed in euros (€). For the high-cost area, US dollars were used as a monetary unit ($1.4 = €1, approximately). US costs were obtained from previous cost-effectiveness articles. Because of the lack of primary and secondary information, indirect costs were not included. Data for major baseline assumptions and costs along with a detailed description of methodology are available online.

### Analysis

The primary evaluation variable was avoidance of recurrent bleeding. Incremental cost-effectiveness ratio (ICER) for upper gastrointestinal hemorrhage avoided was calculated. Mortality was calculated as a secondary variable. All calculations were performed using conventional software (Microsoft Excel XP). One-way sensitivity and multiple-way probabilistic analyses using Monte Carlo simulation for Microsoft Excel XP sensitivity analyses were performed.

**Table 1** Comparative cost, effectiveness, and incremental cost-effectiveness ratio for the different strategies

| Options | Setting | Cost | Effectiveness | ΔC | ΔE | ICER |
|---|---|---|---|---|---|---|
| Test for *Helicobacter pylori* and treatment, if positive | Spain (€) | 909 | 0.93 | 90.7 | −0.01 | Dominated |
| | United States ($) | 3141 | 0.93 | 255 | −0.01 | Dominated |
| PPI maintenance treatment | Spain (€) | 1049 | 0.89 | 230 | −0.05 | Dominated |
| | United States ($) | 3967 | 0.89 | 1081 | −0.05 | Dominated |
| No preventive treatment | Spain (€) | 1121 | 0.82 | 302 | −0.12 | Dominated |
| | United States ($) | 3803 | 0.82 | 917 | −0.12 | Dominated |
| Empirical *H. pylori* eradication | Spain (€) | 819 | 0.94 | — | — | — |
| | United States ($) | 2886 | 0.94 | — | — | — |

ΔC, incremental cost; ΔE, incremental effectiveness; ICER, incremental cost-effectiveness ratio; PPI, proton pump inhibitor.

## Results

The baseline analysis showed that empirical *H. pylori* eradication was the dominant strategy both in the Spanish and the US settings. It was both cheaper and more effective in preventing recurrence of the bleeding ulcer.

Specifically, the 2-year rate of recurrent peptic ulcer bleeding was lower for empirical *H. pylori* eradication strategy (6.1%) than in "test for *H. pylori* and treatment, if positive" (7.4%), "PPI maintenance" (11.1%), and "no preventive treatment" (18.4%). Calculated overall mortality rates secondary to recurrent peptic ulcer bleeding per 1000 patients were 3.6, 4.5, 6.6, and 11.1, respectively. Complete ICER and cost-effectiveness mean values for all four strategies are shown in Table 1.

### *Sensitivity Analysis*

One-way sensitivity analysis showed that none of the variables or costs tested changed the main conclusions of the study. The most influential variable was the prevalence of *H. pylori* in peptic ulcer bleeding. In the high-cost area, when it fell below 45%, "empirical *H. pylori* eradication" strategy was no longer dominant. Nevertheless, it remained cost-effective (ICER <€30,000) until *H. pylori* prevalence in bleeding ulcer fell below 14%, when "PPI maintenance" became the most cost-effective strategy.

By contrast, in the high-cost area, "empirical *H. pylori* eradication" was dominant until the prevalence of *H. pylori* in bleeding peptic ulcer fell below 51%. It remained cost-effective (ICER <$39,000) until prevalence fell below 28%. Below this value, the "test for *H. pylori* and treatment, if positive" strategy became the most cost-effective approach (ICER >$40,000).

The second most influential variable was losses to follow-up. Although "empirical *H. pylori* eradication" remained the dominant strategy, even assuming a zero percent rate of losses to follow-up in any branch, the relative cost-effectiveness of "empirical *H. pylori* eradication" strategy strongly increased as losses to follow-up rose.

Monte Carlo multiple-way probabilistic analyses showed that after 10,000 simulations, "empirical *H. pylori* eradication" was the dominant strategy in 100% of the simulations for both low- and high-cost areas.

## Discussion

Our data strongly suggest that, under a wide range of conditions, "empirical *H. pylori* eradication" is a dominant strategy—that is, it is both cheaper and more effective—than all the remaining strategies evaluated for curing *H. pylori* infection in patients with peptic ulcer bleeding. In addition, this conclusion is fairly robust and remains stable across the plausible variations of costs and assumptions made in the study. Interestingly, despite higher costs, and even assuming lower baseline *H. pylori* infection rates, "empirical *H. pylori* eradication" strategy was nearly as effective in the United States as in lower-cost areas.

"Empirical *H. pylori* eradication" strategy was more effective because all patients with the infection were treated. Testing at endoscopy and retesting negatives are nearly as effective, but a very small percentage of false-negative patients (around 1%) remain. In addition, the "empirical *H. pylori* eradication" strategy avoids a number of visits and tests, thus compensating for the cost of the extra treatments administered. Therefore, it remains the dominant strategy, ahead of others such as the "test for *H. pylori* and treatment, if positive".

The inclusion of losses to follow-up is one of the strengths of the present study. Although even assuming that no patients were lost to follow-up, "empirical *H. pylori* eradication" remains the most cost-effective strategy, the analysis suggests that if empirical eradication truly improves compliance, the cost-effectiveness of the strategy might be even higher than the estimates of this study suggest. It may be especially effective in minorities or patients with a socioeconomically depressed background, which make up a large proportion of the losses to follow-up.

Limitations of the study include the fact that indirect costs (mainly productivity losses) are not included in the analysis and that the values assumed for losses to follow-up are largely hypothetical. Second, the notion that immediate empirical treatment improves compliance, although reasonable, needs to be confirmed in clinical practice. Finally, as the protective effects of *H. pylori* eradication in bleeding are long lasting, a 2-year time horizon probably underestimates the benefits of eradication strategies compared with non-eradication.

In conclusion, our study strongly suggests that "empirical *H. pylori* eradication" strategy associated with PPI prophylaxis in patients remaining on NSAID is the dominant strategy for preventing recurrent peptic ulcer bleeding. The analysis is highly robust and in the sensitivity analysis, the conclusions remain unchanged even with extreme values of the key variables. The results of the pharmacoeconomic model stress the need to confirm the effectiveness of the empirical eradication strategy by clinical studies in patients with bleeding ulcer.

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Supporting information for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

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