

# Importance of post-treatment follow-up to secure sufficient eradication therapy for *Helicobacter pylori*

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## ABSTRACT

**INTRODUCTION:** To optimize the care for *Helicobacter pylori*-associated diseases, we wanted to evaluate the completeness of follow-up after *H. pylori* eradication therapy in a single Danish endoscopy unit. Furthermore, the eradication rates and possible clinical characteristics associated with failure of eradication therapy were considered.

**MATERIAL AND METHODS:** Patients who tested positive for *H. pylori* infection using a rapid urease test (RUT) during a three-year period were evaluated retrospectively according to demographics, eradication rate, type of eradication therapy, endoscopic findings and number of former attempts of eradication therapy. RUT-positive patients without a post-treatment evaluation were invited for a urea breath test.

**RESULTS:** The overall *H. pylori* infection rate was 15% (117/796). Only 48/105 (46%) patients had a post-treatment examination to test the effect of *H. pylori* eradication therapy. The eradication rate by first-line therapy was 75% (58/77). The second-line eradication rate was 87%. 94% (72/77) had the recommended standard triple therapy for first-line eradication therapy. The number of former eradication attempts was the only clinical characteristic that significantly predicted failure of eradication therapy. Among patients with *H. pylori*-positive peptic ulcer, 21/28 (75%) achieved successful eradication after first-line treatment.

**CONCLUSION:** Organised follow-up regimes are recommended, especially in patients with absolute treatment indications with a view to optimizing the care for patients infected with *H. pylori*.

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Infection with *Helicobacter pylori* causes substantial morbidity and mortality in a subset of infected patients [1]. The well-known and extensively studied relation between *H. pylori* and peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma [2] emphasizes the importance of identifying the bacteria in these cases. Furthermore, *H. pylori* eradication produces long-term relief of symptoms in a subgroup of patients with functional dyspepsia, reduces the risk of upper gastrointestinal bleeding in long-term users of nonsteroidal anti-inflammatory drugs (NSAID) and low-dose acetyl salicylic acid ASA, and may finally be

linked to otherwise unexplained iron deficiency anaemia and idiopathic thrombocytopenic purpura [3]. Resent recommendations on *H. pylori* state absolute indications for *H. pylori* evaluation in patients with peptic ulcer, gastric cancer and MALT lymphomas. *H. pylori* evaluation is also suggested in first-degree relatives to patients with gastric cancer and patients with atrophic gastritis, along with the patient groups mentioned above [3]. In clinical trials, failure to eradicate *H. pylori* is approximately 20% after first-line eradication therapy [4, 5], and post-treatment evaluation is therefore recommended to make sure that successful eradication has been achieved [3, 6, 7]. Discordance between the management of *H. pylori*-positive patients in daily practice and clinical trials is obvious. In daily practice, patients are treated by several doctors and instructions are not necessarily similar, compliance is difficult to evaluate and post-treatment follow-up relies on interest and motivation from both patient and clinician. To clarify an expected gap between data in clinical trials and daily practice, we aimed to evaluate the completeness of post-treatment follow-up after *H. pylori* eradication therapy as indicated by the Danish National Guideline for treatment of *H. pylori* [7]. In this guideline, a post-treatment testing is recommended at least in patients with absolute indications for testing and treatment. Furthermore, we wanted to assess eradication rates and identify possible clinical characteristics associated with failure of *H. pylori* eradication therapy.

## MATERIAL AND METHODS

### Study population

Consecutive patients who underwent upper endoscopy and met an indication for rapid urease test (RUT) for *H. pylori* infection as judged by the endoscopist were considered for the study. A total of 769 consecutive patients were tested from 1 January 2008 to 31 December 2010 at the Endoscopic Unit at Amager Hospital, Copenhagen, Denmark, and medical files from patients with a positive RUT were evaluated retrospectively.

### Methods

RUT: Two biopsy specimens (one from the antrum and one from the corpus ventriculi) were analysed from each

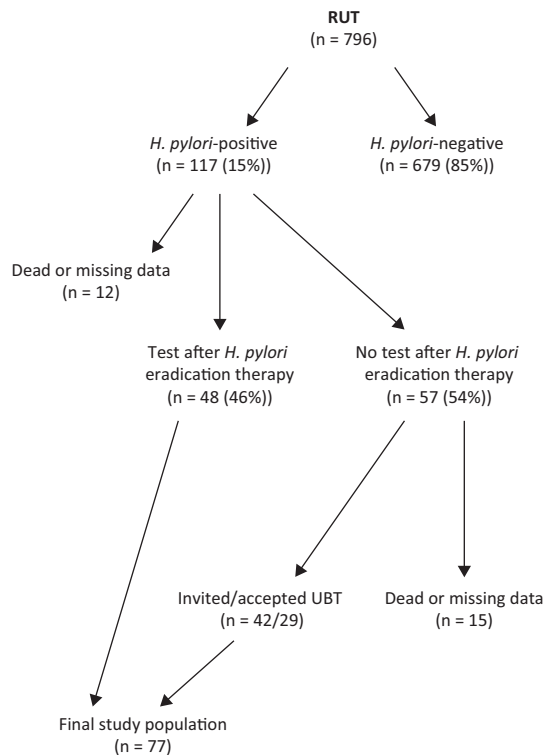
## ORIGINAL ARTICLE

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**FIGURE 1**

Flow chart of the *Helicobacter pylori* infection in overall study population.



RUT = rapid urease test; UBT = urea breath test.

patient, and the RUT (HelicotecUT Plus Urease Test) was used according to the manufacturer's instructions (Strong Biotech Corporation, Taiwan). The colour change within 60 minutes after the biopsies had been placed in the gel was used to check for a positive test.

**Endoscopic diagnosis:** Endoscopic findings were only reviewed for RUT-positive patients. Furthermore, presence of a peptic ulcer was registered for all patients having a RUT, but specific evaluation of the endoscopy report was not done for any of the RUT-negative cases.

**Urea breath test (UBT):** The UBT was performed in a distance of at least seven days from proton pump inhibitor (PPI) treatment and four weeks from antibiotic treatment. Fasting basal and secondary breath samples 30 min after intake of 100 mg <sup>13</sup>C-urea were analysed. A positive threshold was determined when the 30 min ratio was > 5 delta over baseline (DOB) ratio.

**Post-eradication test for *H. pylori*:** Any of the following tests were accepted as a reliable test to evaluate *H. pylori* status after treatment: a RUT during re-gastros-copy, a UBT or histological sample with evaluation of *H. pylori* at microscopy after specific staining [8].

***H. pylori* treatment follow-up:** RUT-positive patients without a post-treatment evaluation were invited by letter (if necessary twice) for a UBT. No RUT-negative pa-

tients, irrespective of endoscopic diagnosis, were invited for a UBT follow-up.

**Study endpoints:** The study population was evaluated in regard to the following endpoints: demographics (age, sex and ethnicity), *H. pylori* eradication rate, type of eradication therapy, endoscopic findings and number of former attempts of *H. pylori* eradication therapy.

***H. pylori* eradication therapy:** The recommended first-line eradication therapy in Denmark is a combination of a PPI, clarithromycin and amoxicillin for seven days or PPI, clarithromycin and metronidazole for seven days (when allergic to penicillin). The recommended second-line treatment is a quadruple treatment with PPI, bismuthsubsalicylate, tetracycline and metronidazole for 14 days. We recorded the prescribed treatment in the study population and compared it to the national recommendations [7].

### Statistics

Calculations were made in 2 × 2 tables using Fishers' exact test in GraphPad Software. A level of less than 0.05 was considered significant.

*Trial registration:* not relevant.

### RESULTS

We found an overall *H. pylori* infection rate of 15% (117/796) in the study population. We were able to evaluate a total of 105 *H. pylori*-positive patients who were offered *H. pylori* eradication therapy (Figure 1). A post-treatment *H. pylori* evaluation was available in 48 cases (46%) (14 RUT, 33 UBT and one histology sample). Fifteen of the remaining patients had died since the initial *H. pylori* test. The remaining 42 patients without a post-treatment evaluation were invited for a UBT. This invitation was accepted by 29 patients resulting in a final study population of 77 subjects.

### Eradication rates

In 58 of 77 patients, the *H. pylori* infection was cured after first-line therapy, resulting in an eradication rate of 75%. Of the 19 patients who were still *H. pylori*-positive, 14 were offered second-line treatment of which nine patients became *H. pylori*-negative resulting in a second-line eradication rate of 87% (67/77). The remaining five *H. pylori*-positive patients, of whom none had ulcer disease, were either judged non-compliant or did not want a second-line treatment due to prior side effects or other reasons. Since only 77 out of 105 patients had a post-treatment evaluation, we estimated the overall best-case eradication rate to 82% (86/105) considering all the patients without a post-treatment evaluation had become *H. pylori*-negative, and vice versa a worst-case eradication rate of 55% (58/105).



*Helicobacter pylori* infected patients need post-treatment evaluation.  
Foto: Bigstock

### Type of eradication therapy

94% (72/77) of patients had the recommended standard triple therapy for first-line eradication therapy. For second-line *H. pylori* eradication, 62% (9/14) had quadruple therapy, the remaining patients had a repeated seven-day triple therapy with another antibiotic combination than first-line therapy along with PPI treatment.

### Clinical characteristics

**Table 1** resumes demographics and clinical characteristics of *H. pylori*-positive cases. As expected, the number of former eradication attempts was the only clinical characteristic that significantly predicted failure of eradication therapy. A total of 167/796 (21%) of the study population were registered as having a peptic ulcer disease (93 gastric ulcer, 58 duodenal ulcer and 16 combined ulcers), 41 (25%) had a positive RUT (**Figure 2**). Data on active bleeding, perforation or other complications were not registered for the RUT-negative cases; all RUT-positive cases had uncomplicated ulcers and no cancers or lymphomas were found.

### *H. pylori* treatment follow-up in peptic ulcer

A post-eradication test for *H. pylori* was available in 28/41 (68%) patients with *H. pylori*-associated ulcer at the initial endoscopy (Figure 2). A total of 20 patients had a post-treatment evaluation (nine UBT, 11 RUT) before the present study and eight of 12 patients still alive at the time of the study accepted an UBT for the purpose of this study. In all, 21 of 28 (75%) *H. pylori*-positive peptic ulcer patients achieved successful *H. pylori* eradication after first-line treatment.

### DISCUSSION

This study reflects the daily clinical management of *H. pylori*-positive patients diagnosed in a standard endoscopy unit during a three-year period. We found that less than 50% of the patients treated for *H. pylori* infection where offered a post-treatment test to clarify whether or not the bacteria had been successfully eradicated. When evaluating the subgroup of patients having *H. py-*

*lori*-associated peptic ulcer disease, 25% of our patients failed eradication at first-line treatment. Only 25% of the ulcer patients were *H. pylori*-positive at the time of initial endoscopy. This could reflect a high rate of false-negative RUTs either due to ongoing PPI treatment or active bleeding as none of these variables were registered prior to RUT. We only focused on the management of *H. pylori*-positive patients and were unable to evaluate further details of endoscopic findings or treatment follow-up of *H. pylori*-negative cases. This stresses the importance of a post-treatment assessment, even in a low-prevalent *H. pylori* area like Denmark, especially in ulcer patients irrespective of *H. pylori* status at the initial testing. Successful *H. pylori* eradication in peptic ulcer disease was shown to reduce the ulcer recurrence rate from about 85% to 20% [9, 10] and furthermore prevents the risk of chronic active gastritis turning into dysplasia [1, 11]. As this knowledge is well established, it was unexpected that only half of the *H. pylori*-positive ulcer patients in our clinical setting had been offered a post-treatment *H. pylori* test. Endoscopy wards commonly serve several different hospital departments (e.g. medical gastroenterology, surgical gastroenterology, internal medicine, paediatrics, etc.) and the follow-up of

TABLE 1

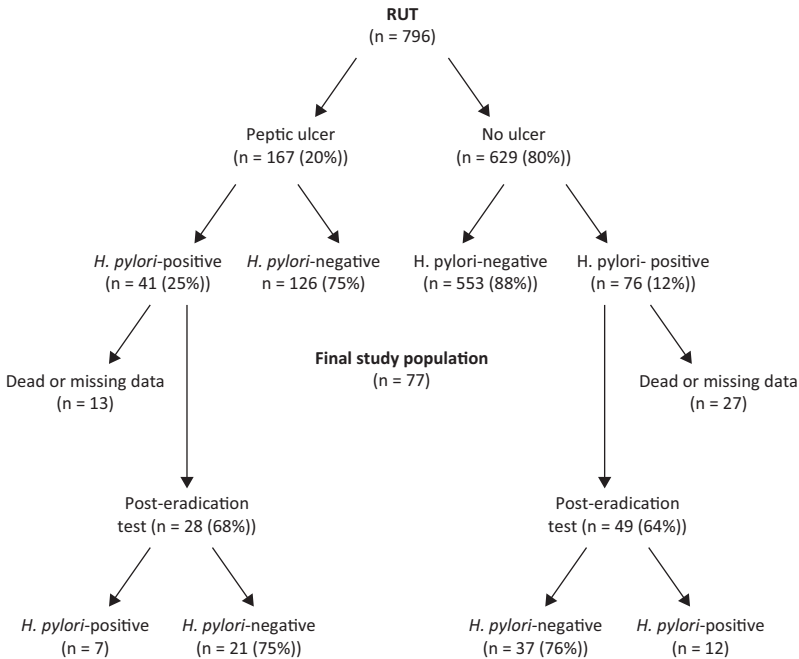
Clinical characteristics of patients presenting with a positive rapid urease test evaluated according to effect of first-line *Helicobacter pylori* eradication therapy. The values are number of patients.

	Successful eradication (n = 58 (75%))	Failure of eradication (n = 19 (25%))	p-value
Female	35	10	0.6
<i>Ethnicity</i>			0.6
Danish	39	11	
All other	19	8	
<i>Age</i>			0.05
≤ 50 years	13	9	
> 50 years	45	10	
<i>Endoscopic diagnosis</i>			1.0
Peptic ulcer	21	7	
No ulcer	37	12	
<i>Type of peptic ulcer</i>			
Duodenal	8	4	
Gastric	12	2	
Combined	1	1	
<i>Eradication treatment</i>			0.2
Clarithromycin/amoxicillin/PPI	52	16	
Other	6	3	
<i>Former eradication treatment</i>			0.004
No treatment	56	15	
1 treatment	1	0	
≥ 2 treatments	1	4	

PPI = proton pump inhibitor.


 FIGURE 2

Flow chart of study population according to presence of peptic ulcer disease and *Helicobacter pylori* test before and after first-line *H. pylori* eradication therapy.



*H. pylori*-positive patients after endoscopy often depends on local interest more than on established procedures for follow-up on *H. pylori*-positive patients. A newly published Canadian study showed that patients diagnosed and treated for *H. pylori* infection during an in-hospital stay had a poorer rate of eradication and a lower rate of post-treatment follow-up than patients treated on an out-patient basis as they were typically given a follow-up appointment along with the prescription of *H. pylori* eradication therapy [12].

In a Danish community-based prospective screening for *H. pylori*, the overall infection rate was 17.5% [13]. In a population of dyspeptic patients presenting in primary care, 28% had a positive test for *H. pylori* [14]. In the present study, 15% of all tested patients were positive for *H. pylori*, which could reflect the retrospective study design without a systematic evaluation of PPI use at time of RUT following a risk of false-negative test results as a possible explanation for the lower infection rate. A previous study showed that ongoing treatment with PPIs resulted in a falsely negative histology for *H. pylori* in almost 30% of cases even when using biopsy specimens from both the antrum and the corpus ventriculi [15].

The recommended first-line triple therapy using PPI in combination with amoxicillin and clarithromycin or metronidazole was given in accordance with the Danish National guideline in 94% of cases. This resulted in an

eradication rate of 75%, which is slightly lower than that observed in previous clinical trials [16]. The eradication rates in our study probably reflect some of the challenges in clinical practice, such as giving the right information, ensuring compliance and follow-up. Only 9/14 of patients got quadruple therapy containing bismuth-subsalicylate for second-line therapy. The number of former treatment attempts seemed to predict another failure to eradicate *H. pylori* infection in our study, but due to the small sample size, the retrospective study design and lack of compliance measurements, this result is of limited value; but antibiotic resistance could be an option. Concerns that increased use of macrolides could cause clarithromycin resistance have been raised as the leading cause for lack of *H. pylori* eradication [17]. In the Scandinavian countries, clarithromycin resistance remains low [17]: a Danish cohort from 1998-2004 evaluating *H. pylori* found 2-3% of cultured *H. pylori* to be clarithromycin-resistant [18]. Newly published data document an overuse of macrolides for upper respiratory tract infections in Denmark; which further increases the risk of development of clarithromycin-resistant *H. pylori* strains [19]. In areas of high clarithromycin resistance (above 15-20%), other treatment regimens like sequential, concomitant or quadruple therapy seem to be superior to clarithromycin-based triple therapy for first-line *H. pylori* eradication [3].

An important element in this trial was to evaluate to which extent the national guidelines were used correctly. Our data indicate that there is room for improvement to achieve better follow-up after treatment, especially in patients with peptic ulcer disease, even in cases with an initial, negative test for *H. pylori*, or other absolute indications for treatment of *H. pylori*. Our data support the use of an organised follow-up regime to fulfil guidelines and avoid missing unsuccessful eradication of *H. pylori* knowing that the recommended eradication therapy is suboptimal [16].

In summary, we found that less than half of the patients treated for *H. pylori* infection were tested after the end of treatment to ensure successful eradication. Organised follow-up regimens are recommended, especially in patients with absolute indications for *H. pylori* treatment. Additional prospective studies are required to identify strategies to improve the care for patients infected with *H. pylori*.

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**CONFLICTS OF INTEREST:** none.

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