Diagnosis and treatment of Helicobacter pylori infection

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This guideline addresses diagnosis and treatment of Helicobacter pylori infection in all types of patients with or without gastrointestinal symptoms, both in primary and secondary care.

WHO SHOULD BE TESTED FOR H. PYLORI?
The recommendations with the associated levels of evidence are summarized in Table 1.

Table 1: Who should be tested for H. pylori?

<table>
<thead>
<tr>
<th>Test indication</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with peptic ulcer disease (gastric ulcer, duodenal ulcer, anastomotic ulcer), previous ulcer disease, gastric cancer (incl. noninvasive cancer) and MALT lymphoma should be tested for H. pylori</td>
<td>Ia</td>
</tr>
<tr>
<td>An H. pylori test-and-treat strategy can be applied to patients with uninvestigated dyspepsia and no alarm symptoms</td>
<td>Ia</td>
</tr>
<tr>
<td>1. degree relatives to patients with gastric cancer should be tested for H. pylori</td>
<td>III</td>
</tr>
<tr>
<td>NSAID-naive patients, who need long-term NSAID therapy, should be tested for H. pylori</td>
<td>Ib</td>
</tr>
<tr>
<td>In cases with unexplained iron deficiency anaemia H. pylori status can be determined</td>
<td>III</td>
</tr>
<tr>
<td>H. pylori testing can be applied in functional dyspepsia, but the symptomatic effect of eradication therapy is modest at best</td>
<td>Ia</td>
</tr>
<tr>
<td>H. pylori infection and/or eradication therapy has no relation to the presence or intensity of GERD</td>
<td>Ib</td>
</tr>
</tbody>
</table>

ABSOLUTE INDICATIONS
- Uncomplicated and complicated peptic ulcer disease (gastric ulcer, duodenal ulcer, anastomotic ulcer)
- Previous ulcer disease
- MALT-lymphoma
- Gastric cancer

COMMENTS
International guidelines [2-4] agree on these indications. In contrast to previous guidelines we now recommend that all patients with duodenal ulcer disease should be tested before eradication therapy because the prevalence of H. pylori among these patients in Denmark and in other western countries is around 40-60% [5-8]. All patients with complicated ulcer disease (bleeding or perforation) must be tested. H. pylori eradication therapy reduces the
risk of new ulcer bleeding (NNT=5) [9, 10] and speeds up ulcer healing after operation for perforated duodenal ulcer [11].

RELATIVE INDICATIONS
- Dyspepsia as part of a “test-and-treat”-strategy
- 1. degree relatives to patients with gastric cancer
- Atrophic gastritis
- NSAID-naive patients who need long-term NSAID therapy
- Functional dyspepsia
- Unexplained iron deficiency anaemia

COMMENTS
H. pylori testing as part of a test-and-treat strategy is suitable for patients with dyspepsia without alarm signs. The strategy is mainly used in primary care. The rationale behind the test-and-treat strategy is, that some of the patients with uninvestigated dyspepsia will have H. pylori-associated ulcer disease and thus will benefit from eradication therapy.

Compared to gastroscopy as the primary strategy to dyspepsia patients without alarm signs the H. pylori-test-and-treat strategy has proven safe and cost-effective [12, 13]. In areas with a low prevalence of H. pylori the symptomatic effect of a strategy based on helicobacter testing will be equivalent to a strategy based on empiric acid suppression [14-16]. As a consequence, these guidelines need revision if the prevalence of H. pylori infection continues to decrease.

The European guidelines (Maastricht III) [4] recommend that first degree relatives to patients with gastric cancer be tested for H. pylori because of a 50% increased risk of cancer in children and a 3-fold increased risk in siblings. The increased risk is primarily mediated by H. pylori infection.

Atrophic gastritis is associated with an increased risk of progression to gastric cancer. However, it is still not confirmed that eradication of H. pylori will reduce the cancer risk [3].

H. pylori and NSAIDs are independent and synergistic risk factors for peptic ulcer and ulcer bleeding [17]. The risk of ulcer in NSAID users is related to the duration of NSAID use but is largest within the first 3 months [18]. Eradication therapy reduces the risk of ulcer disease in NSAID-naive patients whereas this effect can not be demonstrated in chronic NSAID-users [19]. It is unknown how long an NSAID therapy must be before NSAID-naive patients should be offered eradication therapy, but efficacy has been demonstrated after both 8 and 26 weeks of NSAID treatment [19]. There are no studies of the effect of H. pylori eradication in aspirin naive patients.

H. pylori testing – and eradication therapy in infected patients – can be tried in functional dyspepsia but the symptomatic effect is modest at best.

WHO SHOULD BE TREATED FOR H. PYLORI INFECTION?
H. pylori eradication therapy always implies that there is a verified H. pylori infection. The following treatment indications reflect the above indications for testing. If a patient tests positive for H. pylori infection, the patient should be offered eradication therapy regardless of test indication.

INDICATIONS
- Uncomplicated and complicated peptic ulcer disease (gastric ulcer, duodenal ulcer, anastomosal ulcer)
- Previous ulcer disease
- MALT-lymphoma
- Gastric cancer
- Dyspepsia as part of a “test and treat”-strategy
- 1. degree relatives to patients with gastric cancer
- Atrophic gastritis
- NSAID-naive patients, who need long term NSAID therapy
- Functional dyspepsia
- Unexplained iron deficiency anaemia

COMMENTS
Functional dyspepsia (FD) is a very common disorder. There is no effective treatment. H. pylori eradication results in symptom relief in 8-10% of infected patients (NNT 14) [21] and prevents subsequent ulcer development [22].

It has been debated whether infection with H. pylori protects against reflux disease (GERD) and there has therefore been concerns about the possibility that eradication may exacerbate or trigger GERD. There is now evidence that eradication of H. pylori does not affect the frequency of GERD and has no significance for the development of GERD in asymptomatic persons [23-25]. Eradication of H. pylori infection reduces the risk for ulcer but will not eliminate it. Therefore, ulcer prophylaxis is still indicated in high-risk patients in NSAID/aspirin treatment [19, 26].

HOW TO TEST FOR H. PYLORI INFECTION?
The recommendations with the associated levels of evidence are summarized in Table 2.

Table 2: How to test for H. pylori?

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-endoscoped patients can be tested with a urea-breath test (UBT) or a faecal antigen test (FAT)</td>
<td>II</td>
</tr>
<tr>
<td>Endoscoped patients can be tested with a rapid urease test (RUT)</td>
<td>II</td>
</tr>
<tr>
<td>In case of a negative biopsy-based H. pylori test in a patient with ulcer bleeding additional testing for H. pylori must be performed</td>
<td>II</td>
</tr>
<tr>
<td>PPI therapy should be stopped at least 1 week prior to H. pylori testing</td>
<td>II</td>
</tr>
<tr>
<td>Antibiotics should be stopped at least 4 weeks prior to H. pylori testing</td>
<td>II</td>
</tr>
</tbody>
</table>

- Endoscoped patients can be tested with a rapid urease test (RUT)
- Non-endoscoped patients can be tested with a urea-breath test (UBT) or a faecal antigen test (FAT)
- In case of ulcer bleeding the RUT can be false negative. A negative RUT test should lead to additional testing (histology, UBT or FAT)
- Eradication should be checked not earlier than 4 weeks after the end of the eradication therapy
- PPI therapy should be paused not earlier than 7 days and antibiotics at least 4 weeks before testing

COMMENTS
Methods for diagnosis of H. pylori can be divided into invasive (requiring endoscopy and biopsy) and noninvasive tests [27]. Characteristics, advantages and disadvantages are summarized in Table 5.

As a noninvasive test we recommend UBT or FAT, which are equally effective for both primary diagnosis and for monitoring after eradication. As endoscopy-based tests we recommend RUT or histology.
Use of PPIs and antibiotics prior to diagnosis can lead to false negative results. PPI should be paused at least 7 days and antibiotics at least 1 month before H. pylori testing \[2, 4\]. In patients on PPI therapy, the sensitivity is increased by multiple biopsies for RUT and histology from both the antrum and corpus. Control of eradication treatment should be postponed until 4 weeks after completion of the therapy \[2\].

Upper gastrointestinal bleeding leads to decreased sensitivity and specificity of RUT, UBT and stool antigen tests \[28\]. In patients with upper gastrointestinal bleeding it is recommended to take biopsies for RUT. If RUT is negative UBT or FAT must be made at a later stage. Alternatively, additional biopsies for RUT can be made if a control endoscopy is indicated.

### WHAT TREATMENT TO CHOOSE?

The recommendations with the associated levels of evidence are summarized in Table 3.

- **First line therapy:** Triple therapy (7 days) with clarithromycin (500 mg bid) in combination with amoxicillin (1 g bid) or metronidazole (500 mg bid) and PPI (standard dose bid).
- **Second line therapy/after treatment failure:** Quadruple therapy (2 weeks) with PPI (standard dose bid), bismuthsubsalicylate (125 mg, 4 times daily), tetracycline (250 – 500 mg, 4 times daily) and metronidazole (250 mg, 4 times daily).
- **If bismuthsubsalicylate is not available a new triple therapy (2 weeks) with a new combination of antibiotics can be tried:** amoxicillin (1 g bid) or tetracycline (500 mg bid) in combination with metronidazole (500 mg bid) and PPI (standard dose bid).

### Table 3: What treatment to choose?

| All infected patients with peptic ulcer disease (gastric ulcer, duodenal ulcer, anastomosis ulcer); previous ulcer disease, gastric cancer and gastric MALT lymphoma should be offered H. pylori eradication therapy | la |
| First-line treatment is 7-day triple-therapy with PPI and clarithromycine in combination with metronidazole or amoxicillin | la |
| In case of treatment failure quadruple therapy for 2 weeks with bismuthsubsalicylate, tetracycline, metronidazole and PPI is recommended | lb |
| PPI therapy is more effective as ulcer prophylaxis compared to H. pylori eradication therapy in high-risk patients on long term NSAID treatment | lb |

### COMMENTS

Quadruple therapy is more effective as second line therapy than a new triple therapy \[2, 3, 29\]. The eradication rate is increased marginally if treatment length is increased to 10 - 14 days during...
1. If a new triple therapy is recommended for treatment failure the duration should be extended to 14 days [31].
2. Sequential therapy (PPI and amoxicillin for 5 days followed by triple therapy with clarithromycin and metronidazole for another 5 days) can be an alternative after treatment failure, but the evidence for success is sparse in our part of the world.
3. Patients, who have had surgery for bleeding or perforated ulcers, can rarely begin eradication therapy in the immediate postoperative period (newly operated patient etc.). It is recommended to begin treatment in the immediate postoperative period when the patient can eat again. [32]. There is no evidence that rapid eradication therapy decreases the risk of re-bleeding or re-perforation during the current hospitalization.

CONTROL AFTER ERADICATION THERAPY
The recommendations with the associated levels of evidence are summarized in Table 4.

Table 4: Control after eradication therapy

| H. pylori testing should be offered to all patients after eradication therapy | IV |
| All patients with ulcer disease, patients treated for noninvasive gastric cancer and patients with MALT lymphoma must be tested after eradication therapy to ensure successful eradication | III |
| Testing after eradication therapy should be not be done before 4 weeks after treatment has ended | II |
| Urea breath test, faecal antigen test and rapid urease tests or histology of gastric biopsies can be used to check for eradication | II |

- To ensure successful eradication an H. pylori test should be offered to all patients, who have taken eradication therapy
- Patients with an absolute indication for eradication therapy must be tested after the treatment

COMMENTS
Absence of symptoms is an unreliable marker of continuing H. pylori infection after eradication therapy. The eradication rate in primary care in Denmark is estimated at 80%. All patients should be tested to ensure successful eradication. As a minimum, all patients with an absolute indication for eradication therapy (peptic ulcer, MALT lymphoma, surgical treatment of gastric cancer) must be tested 4 weeks after completion of cure. To control the eradication a urea breath test, a stool antigen test or histology can be applied.

REFERENCES
5. Søndergaard B, Bytzer P. H pylori infection is no longer the major cause of peptic ulcer in Copenhagen County. Gastroenterology 2006;130(suppl 2):A268.
16. Ford AC, Moayyedi P, Jarbol DE et al. Meta-analysis: Helicobacter pylori"test and treat” compared with empirical acid


