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CNPHGE
Conseil National Professionnel d'Hépato-Gastroentérologie

APPROPRIATENESS OF CARE

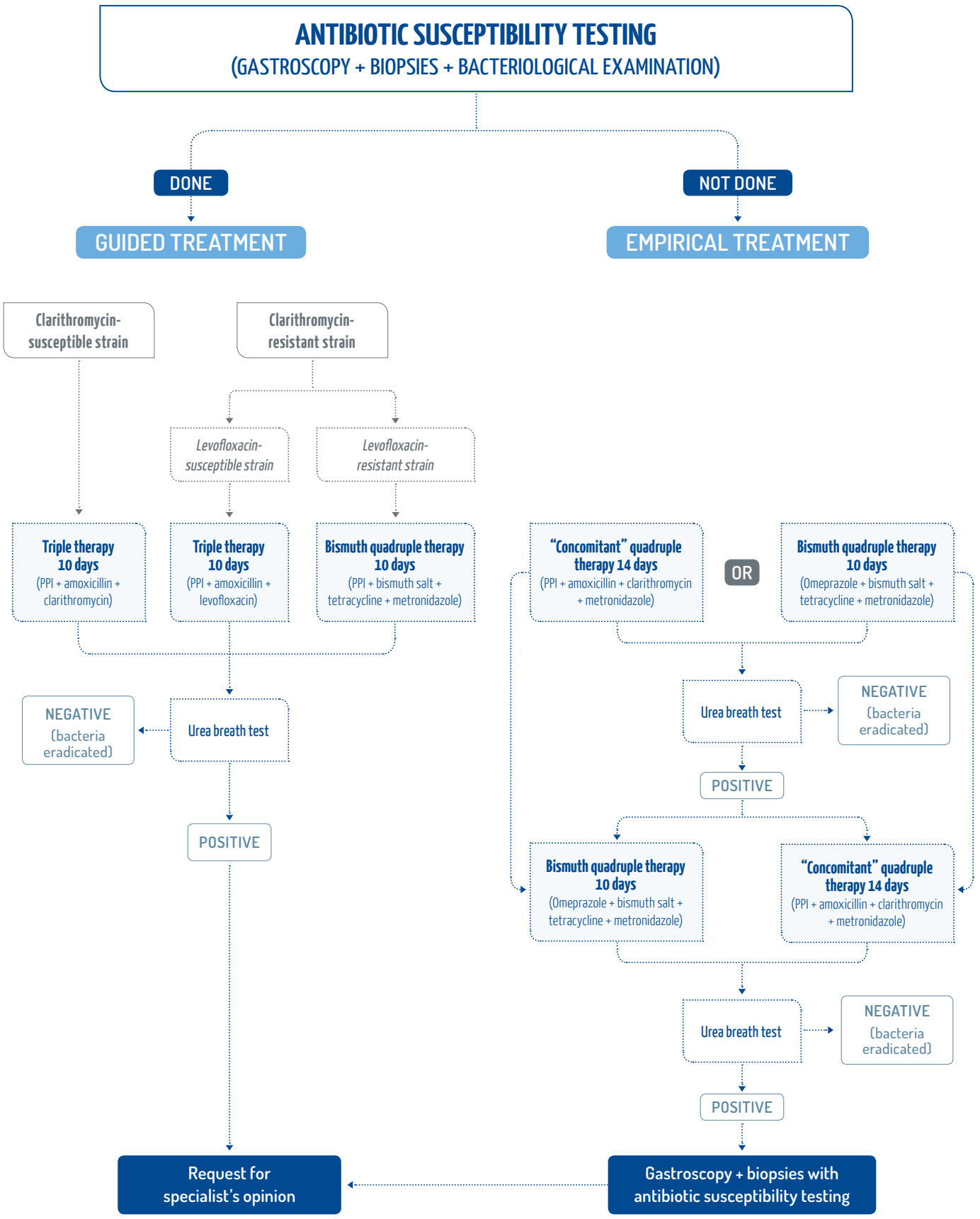
Treatment of *Helicobacter pylori* infection in adults

May 2017

- *Helicobacter pylori* (*H. pylori*) infection plays a major role in the development of gastroduodenal ulcer and gastric cancer (adenocarcinoma and MALT lymphoma). Treatment of the infection demonstrates its efficacy in preventing the occurrence of stomach cancers and recurrences of gastric and duodenal ulcer. It leads to a durable remission of low-level MALT gastric lymphomas. However, progression of bacterial resistance to antibiotics, in particular to clarithromycin (22% of strains), means there is a need to adapt diagnostic and therapeutic practices.
- Practice surveys and database analysis have revealed deviations from the recommended practices. For example, triple therapy combining a proton-pump inhibitor, amoxicillin and clarithromycin is still sometimes prescribed in first-line empirical therapy, prescription of an identical second-line treatment in case of failure may be seen, and eradication control is not always routine.
- This guide is an aid for professionals for making decisions about the treatment of adult patients infected with *H. pylori*. Its aim is to improve the quality of care of patients infected with *H. pylori* and the prevention of gastric cancer and gastroduodenal ulcer, while preserving the bacterial ecology and reducing selection pressure.

- It is essential that the presence of *H. pylori* infection be demonstrated before any eradication treatment.
- Treatment is not urgent: in case of pregnancy or breastfeeding, the treatment must be deferred.
- The treatment should be guided as far as possible based on antibiotic susceptibility, in particular to clarithromycin. In 2017, determining antibiotic-susceptibility of the *H. pylori* strain is based on gastric biopsy culture of making it possible to evaluate susceptibility to all antibiotics and to guide treatment. Gene amplification testing can detect mutations responsible for resistance to clarithromycin, but these tests are not reimbursed.
- In the absence of antibiotic susceptibility testing, treatment will be empirical by default.
- The success of the treatment depends on patient information and involvement (importance of treatment adherence and completion) and the organisation of coordinated care between the gastroenterologist and primary care doctor.

Flowchart for treatment in case of *Helicobacter pylori* infection in adults*



* This flowchart does not apply for women who are pregnant or breastfeeding.

Treatment guided by the antibiotic susceptibility testing

When antibiotic susceptibility testing is available in a patient, the recommended treatment is a guided triple therapy combining a proton-pump inhibitor (PPI) and two antibiotics for 10 days.

- → In case of susceptibility to clarithromycin, prescription of a triple therapy combining a PPI, amoxicillin and clarithromycin.
- → In case of resistance to clarithromycin, prescription of a triple therapy combining a PPI, amoxicillin and levofloxacin, if it is a levofloxacin susceptible strain. If the strain is resistant to levofloxacin, prescription of a bismuth quadruple therapy, combining omeprazole, bismuth salt, tetracycline and metronidazole.
- → In France, one product, Pylera®, is a combination of bismuth subcitrate potassium, tetracycline, and metronidazole. In combination with omeprazole, it has Marketing Authorisation in patients infected with *H. pylori* who have an active gastric or duodenal ulcer or in case of history of ulcer. Pylera® is the subject of an ANSM risk management plan, including in particular an enhanced national monitoring programme, with the objective of monitoring neurological side effects potentially related to bismuth and which may be indicative of bismuth encephalopathy. It is important not to exceed 10 days of treatment. If neurological symptoms occur, it must be discontinued immediately.
- → In case of documented allergy to amoxicillin and a clarithromycin-susceptible strain, prescription of a triple therapy combining a PPI, clarithromycin and metronidazole. In case of documented allergy to amoxicillin and a clarithromycin-resistant strain, prescription of a bismuth quadruple therapy.
- → In case of failure, request for a specialist's opinion (French National Reference Centre for Campylobacters and Helicobacters).

Empirical treatment (in the absence of antibiotic susceptibility testing)

Recommended first-line treatment

- → **"Concomitant" quadruple therapy for 14 days combining a PPI, amoxicillin, clarithromycin and metronidazole.**

  "Concomitant" quadruple therapy replaces "sequential" therapy due to a better efficacy, especially in clarithromycin-resistant strains of *H. pylori*.

  OR

- → **Bismuth quadruple therapy for 10 days combining omeprazole with a bismuth salt, tetracycline and metronidazole**.

  Preference should be given to bismuth quadruple therapy in case of previous use of macrolide or allergy to amoxicillin.

Recommended second-line treatment

- → Do not prescribe again the quadruple therapy used in first line and verify compliance to treatment.
- → In patients who received "concomitant" quadruple therapy in first line, prescription of a bismuth quadruple therapy.
- → In patients who received bismuth quadruple therapy in first line, prescription of a "concomitant" quadruple therapy.
- → After failure of a bismuth quadruple therapy in a patient allergic to amoxicillin, prescription of a treatment guided by the antibiotic susceptibility testing.

In case of failure of eradication after 2 lines of treatment

- → Gastroscopy with biopsies for antibiotic susceptibility testing by biopsy culture.
- → Prescription of a guided treatment based on a specialist's opinion (French National Reference Centre for Campylobacters and Helicobacters).

Dosage of medicines in adults with normal renal function in the studies analysed

- **Amoxicillin:** 1 g BID.
- **Clarithromycin:** 500 mg BID.
- **Levofloxacin:** 500 mg/day QD.
- **Metronidazole:** 500 mg BID.
- **Pylera®:** 3 capsules QID (after meals in the morning, at noon, in the evening and before bed, with a large glass of water) combined with omeprazole 20 mg morning and evening, insisting on the importance of adherence to this QID dosing.
- **PPI:** one dose BID (esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg) during meals.

Precautions

As the information contained in the Marketing Authorisations is subject to change, at the time of the prescription of the product it is advisable to ensure compliance, especially with the contraindications and the warnings and precautions, with a particular focus on drug interactions.

Refer to the information available on the French Public Drug Database, available online at: http://base-donnees-publique.medicaments.gouv.fr.

Routine eradication control at least 4 weeks after the end of treatment

Eradication control must be performed routinely after each line of treatment.

- The urea breath test is a reliable method to check the efficacy of eradication, so long as it is performed at least 4 weeks after discontinuation of antibiotics and at least 2 weeks after discontinuation of PPIs.
- Faecal antigen testing is an alternative to the urea breath test, but this test is not reimbursed.

Patient information and involvement

The patient must be informed by the healthcare professional about:

- *H. pylori* infection and the risks associated with this infection (gastric ulcer, gastric cancer);
- the benefits and risks of the gastroscopy (if it is indicated);
- the efficacy of the proposed treatment;
- the discomforts and side effects of the proposed treatment. These are common, but rarely require discontinuation of treatment: mainly gastrointestinal disorders (including nausea, diarrhoea, vomiting, taste disorder, dyspepsia), headache, dizziness. Other more severe but rare side effects have been described in relation to one or the other of the components of the treatments (refer to the summary of product characteristics available on the French Public Drug Database, accessible by Internet at: http://base-donnees-publique.medicaments.gouv.fr);
- the details of the proposed treatment (molecule, dosage, number of daily doses, time in relation to meals, etc.) and precautions to be taken (awareness of the antabuse effect in case of alcohol consumption when taking metronidazole or Pylera®, preventing photosensitivity when taking levofloxacin or Pylera®);
- the need to take the treatment until completed for optimum efficacy and to notify the physician in case of side effects;
- the importance of eradication control considering the resistance levels observed in France;
- the conditions and methods for performing eradication control by urea breath test:
  - performing the test at least 4 weeks after discontinuation of antibiotics and at least 2 weeks after discontinuation of proton-pump inhibitors,
  - purchase of the urea breath test at the pharmacy,
  - performing the test in fasting conditions at the clinical laboratory,
- the importance of *H. pylori* infection testing in the patient's relatives (parents, siblings, children), in the presence of precancerous or cancerous lesions in the stomach.

Physicians should ensure that the patient properly understands the information provided.

Physicians should also promote their patients' participation in the decision-making process about diagnosis, treatment and follow-up, taking into account their values and preferences.

The method used to develop this guide as well as the literature review are available in the preparation report (available on the HAS website: www.has-sante.fr).

Also available on the HAS website:

- appropriateness guide on "Diagnosis of Helicobacter pylori infection in adults";
- several examples of letters between general practitioner and gastroenterologist to optimise coordination of care;
- an analysis report from private and healthcare administrative databases.

Learn more

- **French National Reference Centre for Campylobacters and Helicobacters**
  www.cnrch.u-bordeaux2.fr/contact – Tél: +33 (0)5 56 79 59 77
- **Website of the French Helicobacter Study Group**
  www.helicobacter.fr

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