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Helicobacter pylori: pathogenesis of infection and management

Francis Mégraud, INSERM U853 and Centre National de Référence des Helicobacters et Campylobacters, Université Victor Segalen Bordeaux 2, F33076 Bordeaux, France.

Pathogenesis

Helicobacter pylori is the leader of a new group of bacteria, the *Epsilonproteobacteria* which have special properties and a particular ecological niche, i.e. the mucus of the human digestive tract. *H. pylori* is the *Helicobacter* adapted to the human stomach and is present in half of the world population. In contrast to the other *Helicobacter* species, it always leads to gastric inflammation and this chronic gastritis which will last during the entire life of the subjects if no intervention occurs.

H. pylori possesses a number of factors which allow its colonisation: urease, adhesins (BabA, SabA), and epithelial cell damage (VacA cytotoxin), and which trigger inflammation (*cag* pathogenicity island [PAI], OipA). While most of the infected subjects will develop minimal symptoms during their lifetime, approximately 10% will suffer from diseases as severe as peptic ulcer disease, gastric MALT lymphoma and gastric adenocarcinoma.

The evolution may be due to host factors, to environmental factors and to bacterial factors because *H. pylori* is a very heterogeneous bacterium. For peptic ulcer disease, blood group A (host factor), smoking (environmental factor) and *cag*PAI (bacterial factor) are the main risk factors. For gastric adenocarcinoma, interleukin-1β polymorphism (host factor), a diet low in vitamins and rich in salt (environmental factor) and again *cag*PAI as well as VacA cytotoxin are the main risk factors. For gastric MALT lymphoma no risk factors have yet been determined.

The *cag*PAI turns out to be very important for *H. pylori*. It encodes a type 4 secretion system allowing the bacterium to inject molecules into the epithelial cell. Among these molecules are muramyldipeptide which binds to NOD receptors and leads to NF-κB activation and production of interleukin 8, a proinflammatory cytokine.

The CagA protein is also introduced and phosphorylated by cell kinases of the Src family, and then interacts with the cell signalling pathways leading to morphological changes in the same manner as that observed in cancer cells.

Despite the sequencing of the whole genome of four strains, it has not been possible to find other new pathogenic factors in *H. pylori*.

Diagnosis

H. pylori infection can be diagnosed by non-invasive tests in young patients without alarm symptoms before being treated. This is the so-called “test and treat” strategy proposed at the Maastricht Conferences in Europe. The recommended test is the urea breath test (UBT), which is accurate and robust. It may not be available in all places, so the antigen stool test, preferably using monoclonal antibodies, is an alternative. Serology, which was originally not recommended, was recognised as a possible test at the Maastricht Update Conference in 2005, because it is the only test which is reliable when the patient has taken proton pump inhibitors (PPI) before consulting the specialist, a currently very common situation in Europe. Other tests based on the identification of antibodies in urine or saliva do not have a sufficient sensitivity to be employed. While this approach has been defined for low *H. pylori* prevalence populations, the procedure may be different for high prevalence groups. When an endoscopy is performed, a rapid urease test is the simplest method for *H. pylori* diagnosis. In patients older that 45 years, a histological diagnosis will allow the detection of pre-malignant lesions, e.g. atrophy and intestinal metaplasia, in addition to *H. pylori*.

Treatment

There are situations where eradication is mandatory, others where treatment is more debatable, but there is a consensus on the treatment regimens to use: PPI (bd), clarithromycin (500 mg bd), and amoxicillin (1 g bd). At the Maastricht 2-2000 Conference, the concept of a treatment package was proposed, i.e. that amoxicillin should be used instead of metronidazole in the first-line therapy in order to avoid the development of resistance to both clarithromycin and metronidazole which would jeopardize the chance of eradication using as a second-line treatment the metronidazole containing bismuth-based quadruple therapy. Omeprazole has been the PPI used primarily from the beginning, and others including esomeprazole have not led to better results. In Western countries the first-line therapy administered for 7 days leads to an eradication rate of 70-80%. In a meta-analysis it was shown that the treatment given for 14 days increased the success rate by 12%. The treatment fails because the antibiotic concentration at the site of the infection is below the minimal bactericidal concentration of the antibiotic against *H. pylori*. This may be because the patient has a poor compliance. It is mandatory for the physician to explain to the patient that he must take the drugs as prescribed and to mention that he will be faced with adverse events, e.g. diarrhoea, bad taste in the mouth, etc. Other causes of failure in a few patients may include lower gastric acidity than usual or a high bacterial load, but the most common by far is *H. pylori* resistance to clarithromycin. A systematic review of the literature has shown that the eradication rate decreased by 70% from 88% when the strain was clarithromycin susceptible to 18% when the strain was clarithromycin resistant.

Clarithromycin resistance varies according to the consumption of this antibiotic in a country, as has been shown in Europe. At the last Maastricht Conference it was said that clarithromycin could be used without testing up to a prevalence of resistance of 15-20%. In the event of failure documented at least four weeks after the end of treatment by a UBT, the second-line treatment to be used is the bismuth-based quadruple therapy, an effective therapy but not convenient to administer. Indeed, the possibility of using this therapy as a "first-line" was accepted in 2005, given the high resistance rate prevalent in certain areas.

Alternative treatments include PPI-amoxicillin-metronidazole, PPI-tetracycline-metronidazole and also an interesting low cost combination i.e. bismuth-tetracycline (or amoxicillin)-furazolidone.

For a third-line therapy, antimicrobial susceptibility testing is required. A favoured combination could be PPI-amoxicillin-levofloxacin, if the strain is susceptible to the new fluoroquinolone, levofloxacin.

Despite a limited armamentarium, it is now possible to eradicate *H. pylori* in more than 90% of patients using two successive therapies and therefore to decrease the burden of chronic diseases.

Selected References for Further Reading

Hatakeyama M, Higashi H. *Helicobacter pylori* CagA: a new paradigm for bacterial carcinogenesis. Cancer Sci 2005;96:835-43.

Malfertheiner P, Mégraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of *Helicobacter pylori* infection - The Maastricht III Consensus Report. Gut 2007;56:772-781

Malfertheiner P, Sipponen P, Naumann M, Moayyedi P, Mégraud F, Xiao SD, Sugano K, Nyren O, Lejondal *H. pylori*-Gastric Cancer Task Force*. Helicobacter pylori* eradication has the potential to prevent gastric cancer: a state-of-the-art critique. Am J Gastroenterol. 2005;100:2100-15.

Mégraud F. *H pylori* antibiotic resistance: prevalence, importance, and advances in testing. Gut. 2004;53:1374-84.

Mégraud F, Lehours P. *Helicobacter pylori* diagnosis and antimicrobial susceptibility testing. Clin Microbiol Rev. 2007;20:280-322.

Michetti P, Suerbaum S. *Helicobacter pylori* infection. N Engl J Med. 2002;347:1175-86.


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