Management of *Helicobacter pylori* Infection: What Should the Surgeon Know?

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Summary

Infection with *Helicobacter pylori* continues to represent a major global health care burden, and various national and international consensus reports and guidelines have aimed at tracking recent developments for their translation into an optimized clinical management. The most important ‘innovation’ is the definition of *H. pylori* gastritis as an infectious disease. This does imply the consideration of therapy of this condition even before the development of clinical manifestations including non-malignant and malignant gastroduodenal diseases, such as peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma. Treatment of *H. pylori* is facing an increasing number of failures, with the main reason being an increasing antibiotic resistance to some of the previously most effective antibiotics, i.e. clarithromycin and levofloxacin, for *H. pylori* strains. Several new treatment options or modifications of already established regimens have been introduced to overcome bacterial resistance and treatment failure. In this review, we provide an update on the current recommendations for a successful management of *H. pylori* infection, and in this context a special reference is made to the role of visceral surgeons.

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Introduction

Over the last three decades the cure of *Helicobacter pylori* infection led to a paradigm shift in clinical medicine with an enormous impact on the daily practice including visceral surgery. *H. pylori*

infection affects more than 4 billion people in the world [1], causes chronic gastritis, and may lead to severe complications, such as peptic ulcer disease, gastric MALT lymphoma, and gastric cancer [2]. A recent estimate assigns around 90% of all gastric cancers to *H. pylori* [3]. Eradication of *H. pylori* cures gastritis and peptic ulcer disease and has the potential to prevent gastric cancer [4]. The identification of the pathogenetic role of *H. pylori* and the successful management of the infection has marginalized the role of surgery in the management of peptic ulcer disease. However, one should keep in mind to test and treat for *H. pylori* when surgery is initially required for complicated peptic ulcer to resolve the life-threatening condition. This review focuses on indications for therapy, diagnostic, and therapeutic management in the context of visceral medicine.

Indications for Therapy

The Kyoto global consensus report on gastritis from 2015 had a significant impact by extending the general indication for *H. pylori* eradication therapy whenever the infection is detected. Consensus was reached in defining *H. pylori* gastritis as an infectious disease irrespective of symptoms and complications [5]. *H. pylori* infection leads to chronic active gastritis in all infected individuals, while the clinical outcome of the infection is unpredictable, ranging from an uncomplicated, clinically unapparent course to most severe complications. In the case of gastric cancer, it is mostly an incurable disease at the time of diagnosis [6]. Similar to other chronic infections such as syphilis or tuberculosis, which may remain clinically silent before eventually presenting with clinical symptoms, the outcome of *H. pylori* infection cannot be predicted for the individual infected and complications, even gastric cancer, are preventable by *H. pylori* eradication [7]. Furthermore, *H. pylori* infection is always transmissible and therefore others are at risk of transmission. Based on this rationale, *H. pylori* gastritis requires therapy in all cases if there are no serious objections concerning a specific individual case.

Table 1. Recommendations for *Helicobacter pylori* eradication

Duodenal/Gastric ulcer (active or not, including complicated peptic ulcer disease)
MALToma and diffuse large B-cell lymphoma
Atrophic gastritis
After gastric cancer resection
First-degree relatives of patients with gastric cancer
<i>Helicobacter pylori</i> test and treat in case of <i>uninvestigated</i> dyspepsia
Lymphocytic gastritis
<i>Helicobacter pylori</i> test and treat in case of unexplained iron deficiency anemia
<i>Helicobacter pylori</i> test and treat in case of idiopathic thrombocytopenic purpura
Before long-term use of aspirin and nonsteroidal anti-inflammatory drugs in patients with ulcer history

Eradication of *H. pylori* heals and restores the inflamed mucosa; however, in case of premalignant conditions such as intestinal metaplasia and atrophic gastritis, already established complete reversibility is rarely accomplished and these patients need to be included in regular endoscopy-based follow-up [8].

H. pylori eradication therapy also offers benefits concerning the social health-economic aspect as it i) reduces the risk of transmission and ii) avoids costs that are associated with complications of diseases related to *H. pylori*.

All these facts lead to the recommendation in the Kyoto consensus report that individuals infected with *H. pylori* should be offered eradication therapy, unless there are competing considerations.

This comprehensive recommendation also asks the question about the optimal timing of eradication in asymptomatic subjects and concludes that eradication therapy should be offered and grants the maximum benefit if it is performed while the mucosal damage is still non-atrophic.

Most current guidelines are adopting this principal concept of the Kyoto consensus reports. The German guideline of 2016 states that patients with asymptomatic *H. pylori* gastritis should be offered eradication therapy [9]. The European Maastricht V/Florence consensus report reemphasizes *H. pylori* gastritis as an infectious disease irrespective of symptoms and complications [10].

Although all recent guidelines simplified indications for *H. pylori* eradication therapy in a way that all infected should undergo eradication therapy unless competing interests suggest otherwise, it is important to recapitulate the so-called classical indications. These are summarized in table 1.

Diagnosis of *Helicobacter pylori* Infection

Diagnosis of *H. pylori* infection is made by using non-invasive and invasive methods. Urea breath test (UBT) and stool antigen test (SAT) are the two recommended non-invasive test methods in clinical practice and have a comparable sensitivity and specificity with the endoscopy-based tests [11]. In general, UBT is the best ac-

cepted approach for diagnosis [12]. The most important clinical aspect to consider when testing with UBT and SAT is the mandatory discontinuation of therapy with proton pump inhibitors (PPI) 2 weeks prior to testing in order to avoid false-negative results. Whether a 7-day withdrawal may be sufficient remains uncertain. Following bismuth compounds and antibiotics, a 4-week discontinuation before testing is mandatory. Antacids and H2-blockers do not impair the sensitivity of UBT and SAT [13].

Serology with detection of *H. pylori* antibodies cannot distinguish between active infection and previous exposure and therefore is not a test for clinical routine. Due to the detection of antibodies, which can remain positive for a long time even after successful treatment, serology can increase the number of false-positive results. Under certain clinical circumstances such as gastrointestinal bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric cancer, there is an expected low bacterial load, leading to a decreased sensitivity of all diagnostic methods except for serology. Thus, serology has its value in this situation.

All invasive test methods require endoscopy with biopsies and comprise the rapid urease test (RUT), histology, and culture. RUT is the first-line diagnostic test when endoscopy is indicated, and there is no contraindication for biopsy. The test provides an excellent sensitivity and specificity (90–100%), and in case of a positive result immediate treatment is allowed. False-negative results can occur during a bleeding episode as well as during the use of PPI, antibiotics, or bismuth compounds. The same applies to advanced atrophy or intestinal metaplasia. False-positive results are quite unusual, and guidelines recommend one biopsy from the antrum and one from the corpus region of the stomach.

Histology is the standard diagnostic tool for *H. pylori* assessment. Besides *H. pylori* detection, histology qualifies the degree of inflammation and reports on atrophy/intestinal metaplasia, dysplasia, and malignancy [14]. For the assessment of *H. pylori* gastritis, standard biopsy should include two biopsies from the antrum and two biopsies from the middle of the corpus. Furthermore, an additional biopsy from the incisura angularis should be taken for the detection of precancerous lesions [15]. *H. pylori* infection can be diagnosed in most cases by histochemical staining alone. In case of expected low density of the bacteria, however, immunohistochemical staining for *H. pylori* can be performed to improve the yield of histological assessment [16]. Therefore, the European guidelines recommend to use immunohistochemistry in cases of chronic gastritis and atrophic gastritis or during follow-up after eradication therapy for *H. pylori* when no organisms are identified by using histochemical stains. It must be noted, however, that immunohistochemistry is more expensive than histochemical stain and is not available in all laboratories.

Culture is the gold standard for the detection of bacterial infections, but not in case of *H. pylori* infection. The reason for this is the prolonged incubation period of up to 2 weeks. The value of culture of *H. pylori* is primarily to perform antibiotic sensibility testing for commonly used antibiotics in the treatment of the infection in order to identify potential antibiotic resistance and to select an alternative treatment regimen after two failed eradication tries.

Fig. 1. Treatment algorithm based on the German guideline.
*Risk factors: country of origin, pretreatment with macrolides.

Treatment of *Helicobacter pylori* Infection

The efficacy of the standard first-line PPI-based triple therapy in most parts of the world has continuously decreased in the past years. There are several reasons for the loss of eradication efficacy. By far most important is the increasing rate of *H. pylori* resistance to antibiotics. The resistance to clarithromycin has the highest impact on treatment failure, and the according rate of resistance has dramatically risen in many countries.

The resistance to clarithromycin varies between populations and shows regional differences. For example, in Austria a resistance rate of around 30% is described, while the resistance in Germany is still in the order of or even below 10% [17, 18].

To overcome treatment failure with PPI standard triple therapy, various regimens have been tested and introduced, including sequential and quadruple therapies and various combinations of antibiotics.

PPI/clarithromycin-based triple therapy should be abandoned when clarithromycin resistance in the region is known to be more than 15%. In areas with a high clarithromycin resistance (>15%) several treatment options are available. In this case a bismuth-containing quadruple therapy or a concomitant quadruple therapy should be used as first-line treatment. In areas of high dual resistance to both clarithromycin and metronidazole, bismuth-based quadruple therapy represents a valid first-line option. The same recommendation applies to areas with low clarithromycin resistance. In this scenario, however, PPI/clarithromycin-based triple therapy is also an alternative.

A novelty of the current treatment recommendations is the extension of treatment duration. All therapy regimens should be

given for 14 days, unless 10-day therapies are proven to be effective in the region. The reason for the prolongation of therapy is based on the results of a recent Cochrane systematic review and the analysis of 75 studies [19].

In case of therapy failure of first-line treatment, second-line treatment is based upon first-line treatment with the goal to avoid already used antibiotics. After failure of bismuth-containing quadruple therapy, a fluorchinolone-based triple therapy should be applied. In case of failure of PPI/clarithromycin-based triple therapy, a bismuth-containing quadruple therapy is a valid second-line treatment. The last scenario is a failure of non-bismuth-based quadruple therapy. European guidelines recommend either a bismuth-containing quadruple therapy, a fluorchinolone-based triple therapy, or quadruple therapy for this scenario.

Second-line treatment failure requires antibiotic susceptibility testing after culture of *H. pylori*. Rescue treatment after failure of second-line treatment requires guidance by antibiotic susceptibility testing. Fig. 1 proposes a treatment algorithm based on the German guideline.

Surgery and *Helicobacter pylori*

Surgery played a predominant role in the treatment of peptic ulcer disease in the pre-*H. pylori* era. Surgical procedures dominated the field of ulcer therapy for a century with the development from respective procedures into more and more detailed interventions on the vagal nerve [20]. Since the late 1980s, the need for surgery in the treatment of ulcer disease has dramatically decreased. Surgery beyond endoscopy and invasive radiological interventions

for ulcer bleeding is rarely required nowadays. However, ulcer perforation and gastric outlet obstruction uphold the demand for surgical intervention. In all these conditions, *H. pylori*-related ulcer disease needs to be considered, and surgeons need to remain aware of the necessity of testing for *H. pylori* to prevent recurrence and further complications of the disease [20].

The core field of surgery these days is related to gastric cancer, and in this context it is recommended to encourage relatives of patients with gastric cancer to present for *H. pylori* testing and therapy in case they are found to be infected.

In relation to screening for colorectal cancer, a further approach we would like to bring to attention is the chance to simultaneously screen for gastric cancer. Colorectal cancer screening via colonoscopy is an established strategy for disease prevention. In contrast, there is no population-based screening for gastric cancer in countries with low to moderate incidence rates of the disease. A 'serological biopsy' with the determination of serum pepsinogens I and II (sPG-I and sPG-II), sPG-I/II ratio, and anti-*H. pylori* antibodies (IgG-*Hp*) allows to identify patients with preneoplastic changes (intestinal metaplasia/atrophic gastritis) of the gastric mucosa that are at increased risk for gastric cancer and who would benefit from a diagnostic gastroscopy [21]. In a prospective study we are currently trying to evaluate the use of 'serological biopsy' in order to identify patients with preneoplastic conditions of the gastric mu-

cosa undergoing colonoscopy. This novel approach with the combination of screening colonoscopy and the 'serological biopsy'-based strategy should be considered for gastric cancer screening.

Conclusion

The implementation of *H. pylori* therapy has revolutionized the clinical practice in visceral medicine. Peptic ulcer disease has become curable by *H. pylori* eradication therapy. For non-*H. pylori*-related peptic ulcers, PPI are the standard of care. Furthermore, *H. pylori* eradication offers the chance to prevent gastric cancer [22]. Recent guidelines and consensus recommendations state that *H. pylori* gastritis is an infectious disease. This has a high impact on treatment indications. The challenge for the present and future remains to adopt the best available treatment regimen and to continue to optimize therapies for successfully overcoming the increasing resistance of *H. pylori*. The search for a vaccine – with partial success already achieved – should not be abandoned.

Disclosure Statement

The authors have no conflicts of interest to declare.

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