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Mini Review

Historical Overview of the Maastricht Consensus Reports for the Management of *Helicobacter Pylori* Infection. Where are we Today?

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Abstract

This letter summarizes historical overview of the European guidelines for management of *Helicobacter pylori* (*H. pylori*) infection, from Maastricht I consensus report through to Maastricht V/Florence consensus report. The inadequate application of Maastricht V/Florence consensus report in clinical practice has urged us to send an appeal to all national gastroenterological societies to emphasize the importance of these guidelines.

Keywords: Maastricht consensus report; *Helicobacter pylori*; Guidelines; Primary care physicians; History

Introduction

This mini review summarizes historical overview of the European guidelines for management of *Helicobacter pylori* (*H. pylori*) infection, from Maastricht I consensus report through to Maastricht V/Florence consensus report. The inadequate application of Maastricht V/Florence consensus report in clinical practice has urged us to send an appeal to all national gastroenterological societies to emphasize the importance of these guidelines.

Insufficient level of knowledge and lack of adherence of Primary Care Physicians (PCPs) to the guidelines for the management of *H. pylori* infection has been observed through the last three decades. European *H. pylori* study group was established in 1987. Experts in the field of *H. pylori*, primary care physicians and representatives of National Societies of Gastroenterology from Europe have organized a meeting in Maastricht to establish consensus guidelines on the management of *H. pylori* at the primary care and specialist level.

Historical Overview of the Maastricht Consensus Reports

According to the first Maastricht consensus report published in 1997. recommended 1st-line therapy was triple therapy for 7 days, and indication for eradication *H. pylori* were: all *H. pylori* positive patients with peptic ulcer disease, past or present; bleeding peptic ulcer; infected patients with low grade gastric MALT lymphoma; in cases with advanced and progressively worsening forms of gastritis, such as in patients with intestinal metaplasia, glandular atrophy and those with erosive or hypertrophic forms of gastritis; after resection of early gastric cancer or precancerous lesions. Advisable eradication of *H. pylori* was for: functional dyspepsia (after full investigation), family history of gastric cancer, long term treatment with proton pump inhibitors for *gastroesophageal reflux disease*(GERD), planned or existing NSAID therapy, following gastric surgery for peptic ulcer, if the patient's wishes [1] (Table 1).

The Maastricht 2-2000 Consensus Report was produced in 2000. Recommended first-line therapy by the guidelines was triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole for a minimum of 7 days. Second-line therapy was quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline for a minimum of 7 days [2] (Table 1).

The Maastricht III Consensus Report was produced in 2005 and published in 2007. The strength of recommendations (A, B, C, D) and evidence (level from 1-5) to support them were graded. *H. pylori* eradication is an appropriate option for patients infected with *H. pylori* and investigated non-ulcer dyspepsia (A, 1a). Routine testing for *H. pylori* is not recommended in GERD (A, 1b). PPI-clarithromycin-amoxicillin or metronidazole treatment remains the recommended first choice treatment in populations with less than 15–20% clarithromycin resistance prevalence. PPI-clarithromycin-metronidazole is preferable in populations with less than 40% metronidazole resistance prevalence. Quadruple therapies are alternative first choice treatments. The same first choice *H. pylori* treatments are recommended worldwide, although different doses may be appropriate [3].

The Maastricht IV/ Florence Consensus Report was produced in 2010 and published in 2012. According to this consensus ^{13}C urea remains the best test to diagnose *H. pylori* infection. The diagnostic accuracy of the Stool Antigen Test (SAT) is equivalent to the UBT if a validated laboratory-based monoclonal test is used. In areas of low clarithromycin resistance, clarithromycin- containing treatments are recommended for first-line empirical treatment. Bismuth-containing quadruple treatment is also an alternative. In areas of high clarithromycin resistance, bismuth containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available sequential treatment or a non-bismuth quadruple treatment is recommended. The use of high-dose (twice a day) PPI increases the efficacy of triple therapy. Extending the duration of PPI-clarithromycin-containing triple treatment from

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Table 1: Brief summary of Maastricht Consensus Reports.

Name of consensus, year of production and structure of the meeting	Recommended 1st-line therapy	Recommended 2nd-line therapy	Indication for eradication *H. pylori* + -Strongly recommended	Recommended diagnostic tests	Confirmation of eradication
Maastricht Consensus Report, 1996, 63 participants from 19 European countries as well as observers from Canada, Japan and the USA.	triple therapy for 7 days, using a proton pump inhibitor and two of the following: clarithromycin, a nitroimidazole (metronidazole or tinidazole) and amoxycillin	re-treatment regimen should be selected after consideration of previous treatment or microbial sensitivities, or both. Additionally, quadruple therapy (omeprazole plus classic bismuth based triple therapy) can be used in the event of failure of triple therapy.	Peptic ulcer disease (whether active or not) Bleeding peptic ulcer Low grade gastric MALT lymphoma; Gastritis with severe abnormalities Following early resection for gastric cancer	^{13}C-urea breath test (UBT) Laboratory serology is also strongly recommended, It is strongly recommended, that patients over 45 years who have severe dyspeptic symptoms, and those with alarm symptoms (irrespective of age) should be referred to a specialist for endoscopy.	The "gold standard" is the ^{13}C-UBT; no earlier than 4 weeks after cessation of treatment; in complicated peptic ulcer disease,gastric ulcer, cases of low grade gastric MALT lymphoma, where treatment is incomplete and when compliance is poor.
Maastricht 2-2000 Consensus Report, 2000. 76 participants from 28 countries. Maastricht III Consensus Report, 2005, 50 experts from 26 countries	triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole for a minimum of 7 days PPI-clarithromycin-amoxicillin or metronidazole treatment remains the recommended first choice treatment in populations with less than 15–20% clarithromycin resistance prevalence. In populations with less than 40% metronidazole resistance prevalence PPI-clarithromycin-metronidazole is preferable. Quadruple therapies are alternative first choice treatments.	quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline/ minimum 7 days. Where bismuth is not available, 2nd-line therapy should be with proton pump inhibitor-based triple therapy Bismuth-based quadruple therapies remain the best second choice treatment, if available. If not, a PPI, amoxicillin or tetracycline and metronidazole are recommended.	Peptic ulcer disease (active or not, including complicated ulcer); MALToma; Atrophic gastritis; post-gastric cancer resection; Patients who are first-degree relatives of gastric cancer patients; Patients' wishes (after full consultation with their physician) Duodenal/gastric ulcer (active or not, including complicated PUD) MALToma Atrophic gastritis After gastric cancer resection; Patients who are first degree relatives of patients with gastric cancer Patient's wishes (after full consultation with their physician)	urea breath test or stool antigen test UBT and the stool antigen tests; Certain kits for serology with high accuracy can also be applied	Always test for successful eradication, by urea breath test or endoscopy-based test if endoscopy is clinically indicated. Stool antigen test is the alternative if urea breath test is not available UBT if available. when a UBT is not available, a stool test can be used. Confirmation of H pylori eradication should be performed at least four weeks after treatment
Maastricht IV/ Florence Consensus Report, 2010, 44 experts from 24 countries	In areas of low clarithromycin resistance: clarithromycin-amoxicillin/metronidazoletherapy (10-14 days) or bismuth-containing quadruple treatment. In areas of high clarithromycin resistance: bismuth-containing quadruple treatments, sequential treatment or concomitant treatment.	bismuth containing quadruple therapy orlevofloxacin containing triple therapy	All *H. pylori* positive patients	UBT and the stool antigen tests. There is no role for serology.	The UBT or a laboratory-based validated monoclonal stool test are both recommended as non-invasive tests. The time for testing the success of H pylori eradication after the end of treatment should be at least 4 weeks.
Maastricht V/ Florence Consensus Report, 2015,43 experts from 24 countries	In areas of low clarithromycin resistance, triple therapy. In areas of high (>15%) clarithromycin resistance: bismuth quadruple(BQT) or concomitant therapies. In areas of high dual clarithromycin and metronidazole resistance, BQT is the recommended.Duration: 14 days, unless 10days therapies are proven effective locally.	bismuth-containing quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy	All *H. pylori* positive patients	UBT is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'. Monoclonal SAT can also be used.	UBT and the stool antigen tests, at least 4 weeks after completion of therapy.

7 to 10-14 days improves the eradication success by approximately 5% and may be considered. PPI-clarithromycin-metronidazole and PPI-clarithromycin-amoxicillin regimens are equivalent. According to the guidelines, *H. pylori* eradication to prevent gastric cancer was considered in the following: first-degree relatives of family members with a diagnosis of gastric cancer; patients with previous gastric neoplasia already treated by endoscopic or subtotal gastric resection; patients with a risk of gastritis: severe pan-gastritis, corpus-predominant gastritis, severe atrophy; patients with chronic gastric acid inhibition for more than 1 year; patients with strong environmental risk factors for gastric cancer (heavy smoking, high exposure to dust, coal, quartz, cement and/or work in quarries); *H. pylori*-positive patients with a fear of gastric cancer. [4].

The last Maastricht V/Florence consensus Report was produced in

2015 and represents the current guidelines [5]. (Table 1). According to the consensus clarithromycin triple therapy as 1st line-therapy is not recommended for countries with a high rate of resistance to clarithromycin such as Croatia. Unfortunately, this was the choice of 66.3% Croatian PCPs [6]. All previous studies found that triple therapy with amoxicillin and clarithromycin was the most commonly prescribed therapy which is not in accordance with the consensus. The knowledge of some physicians is at the level of Maastricht I consensus. The first attempt to eradicate *H. pylori* infection is the most important one since the rate of resistance to antibiotics clarithromycin and metronidazole increases with each successive attempt of *H. pylori* eradication. Insufficient level of knowledge in regards to the first line therapy is also a factor of secondary resistance to clarithromycin and metronidazol.

Conclusion

H. pylori infection is a global problem and poor adherence to the guidelines is an alarming problem. With this article we want to point out the importance of better engagement of national gastroenterological societies in the EU and the world as well as to encourage better cooperation with associations of family physicians. The publication of guidelines is an important measure. However, the publication of the guidelines in itself does not guarantee the application of its principles in clinical practice. Maastricht Consensus Reports are extensive scientific reports about *H. pylori* infection. National gastroenterology societies should present to PCPs shorter overview of the key points and the most important recommendations of the guidelines depending on the regional resistance rate of *H. pylori* to antibiotics.

We are looking forward to new guidelines and recommendations for *H. pylori* infection.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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