The Maastricht III consensus : summary and comments

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Abstract

The management of *Helicobacter pylori* infection as been readapted to recent information which resulted in new guidelines that were published in 2007 in Gut. Iron deficiency anemia with negative work up and idiopathic thrombocytopenic purpura were added to the indications for treatment while the known ones were reconfirmed. Much interest went to prevention of gastric cancer and treatment. In the prevention of gastric cancer the importance of treating infected individuals before the appearance of premalignant lesions was highlighted. The most important problem concerning treatment is the increasing resistance for clarithromycin with as a consequence a decreasing efficiency of the classical therapy. Alternatives are discussed and results of resistance for different antibiotics in Belgium are presented. (Acta gastroenterol. belg., **2009**, 72, **344-349**).

The European Helicobacter Study group, founded in 1987, published new guidelines on the management of *Helicobacter pylori* (*H. pylori)* in the September issue of Gut in 2007 (1). This was already the 2nd adaptation from the initial guidelines which were issued in 1997, the first adaptation being published in 2002 (2,3). The publication in Gut in 2007 was the result of the consensus meeting held in 2005. The last Belgian consensus meeting on *H. pylori*-related diseases dates from 1998 (4).

Although the most active area of research of the European Helicobacter Study group is into the link between *H. pylori* and gastric cancer, recommendations are formulated on different issues. Besides treatment recommendations, a lot of associated statements are included in this consensus.

The strength of the recommendations is graded but the grade of recommendation does not always match the level of evidence because of conflicting results in the literature and different interpretations of the studies by the experts.

Statements and recommendations are presented on diagnosis, treatment, prevention of gastric cancer and relation with dyspepsia, gastro-esophageal reflux disease (GERD), intake of non-steroidal anti- inflammatory drugs (NSAID) and extra-intestinal manifestations. The absolute indications for eradication have been reconfirmed, the most important ones stay the prevention of recurrence of ulcer disease, the prevention of gastric cancer and, added in the last guidelines, idiopathic thrombocytopenic purpura (ITP) and unexplained iron deficiency anemia in patients in whom other causes have been excluded (5,6).

Absolute indications for treatment :

- Ulcer disease, active or not
- Low grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma confined to the mucosa/ submucosa (Lugano stage I) and in the absence of specific gene translocations *
- Atrophic gastritis
- After gastric cancer resection
- First degree relatives of patients with gastric cancer

The last recommendations added

- Unexplained iron deficiency anemia
- ITP

both with a good level of evidence based on placebo controlled trials

* gene t (11,18) (q21;q21) with fusion of API2 and MALT1

The guidelines also include patient's whishes with a strong grade of recommendation but without scientific evidence.

In primary care for **dyspepsia**, a "test and treat" strategy is cost-beneficial and still recommended in adults below the age of 45 (the age can vary between countries, depending of the prevalence of gastric cancer). The benefit is modest as can be expected when conflicting data exist in literature (7,8). Furthermore, in areas of decreasing prevalence (< 20%), like in the western world, empirical treatment with proton pump inhibitors (PPI) is an equivalent option (9).

Eradication in patients with **GERD** is still to be considered if long term PPI intake is indicated, in order to prevent atrophic gastritis. In this case, recommendations are based on individual cohort studies.

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Although it is accepted in the consensus that eradication of *H. pylori* does not cause GERD and does not decrease the efficacy of the PPI therapy, it can not be denied that there is a clear negative association between the prevalence of *H. pylori* and GERD, Barrett and adenocarcinoma of the cardia. Furthermore, the consensus states also that severe inflammation involving the fundus and the stomach, is associated with reduced gastric secretion and is inversely correlated with GERD and its complications. However, patients who will be more prone to develop reflux will be those with a predominantly corpus gastritis, the most dangerous form of gastritis in the development of gastric cancer. Furthermore, it must not be forgotten that gastric cancer is still much more frequent than adenocarcinoma of the esophagus. In conclusion it can be said that, since safe and potent drugs exist for the treatment of GERD it seems unjustified to leave a potentially dangerous organism untreated.

The interaction between *H. pylori* and **NSAID** is complex. It is established that *H. pylori* and NSAID both independently increase the risk of peptic ulcer bleeding. The risk of bleeding is increased by about 6 fold when both factors are present (10). The effect of eradication on the development of ulcera in patients taking NSAID therefore will depend on the proportion of true *H. pylori* ulcera. It has been shown that in the prevention of upper gastrointestinal bleeding in NSAIDs users, maintenance treatment with proton pump inhibitors (PPI) is better than *H. pylori* eradication alone. Therefore, eradication is to be recommended in chronic NSAID users since the best treatment to prevent bleeding is PPI and in long term PPI users, eradication is indicated in order to prevent atrophy.

Eradication should also be given to long term aspirin users with a history of bleeding ulcers.

H. pylori and **gastric cancer** :

H. pylori infection is the most common proven risk factor for non-cardiac gastric cancer with host genetic factors and environmental factors contributing to the risk.

Nowadays, no one doubts the fact that eradication of *H. pylori* improves the histology of the stomach and prevents the development of pre-neoplastic changes (11). Concerning the effect on the prevention of gastric cancer however, the results are conflicting (12,13,14) . This is due to the fact that, in the evolution from metaplasia to gastric cancer, it is unknown where the point of no return is situated. This also explains the results of multiple studies, mainly from Asian countries with a high incidence of gastric cancer, where no benefit can be shown from *H. pylori* eradication on the development of gastric cancer in the total patient group but where subanalyses, considering only patients without precancerous lesions, show that *H. pylori* eradication clearly decreases the risk of gastric cancer development (15,16,17,18).

The consensus report concluded that eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development with the optimal time being before pre-neoplastic lesions are present. It is also stated that eradication for gastric cancer prevention in populations at risk should be evaluated and considered. In populations with a high incidence of *H. pylori* gastritis, cost effective analyses show a benefit of primary prevention eradication in young patients (19). In developed countries these cost-effective analyses are less convincing (20,21).

In Belgium gastric cancer (cardiac and non-cardiac cancer) represents ± 3% of the total cancer burden in Belgium (Table 1). Cervical cancer represents 1.5% of all cancers. Of course, although both are deadly diseases, *H. pylori* associated gastric cancer can be expected to decrease, what is probably not the case for cervix cancer. Nevertheless, the information from the studies in Asia should stimulate eradication in young patients.

The diagnosis of *H. pylori* :

No major changes were made in the comments on diagnosis. The most reliable non invasive tests are the ^{13}C-Urea Breath Test (UBT) and the stool test with accuracy ranging between 90 and 99% (22,23). The stool test is better when monoclonal antibodies are used in stead of polyclonal antibodies. If endoscopy is performed, a rapid urease test has an accuracy superior to 90% within 1 hour.

The problems of the UBT and stool test are often the availability. The UBT test is not always reimbursed or available. The stool test is usually performed only in laboratories with high volume testing due to the batch testing. This means that stools must be stored at -20 °C until enough samples are collected. Individual testing kits are now coming to the market.

Serology to assess *H. pylori* infection is recommended in conditions associated with low bacterial density (MALT lymphoma, atrophy) and in bleeding ulcers (in bleeding ulcers the performance of the above mentioned tests is decreased). However, it is recommended to repeat UBT or stool test if there is a discrepancy between these tests and serology.

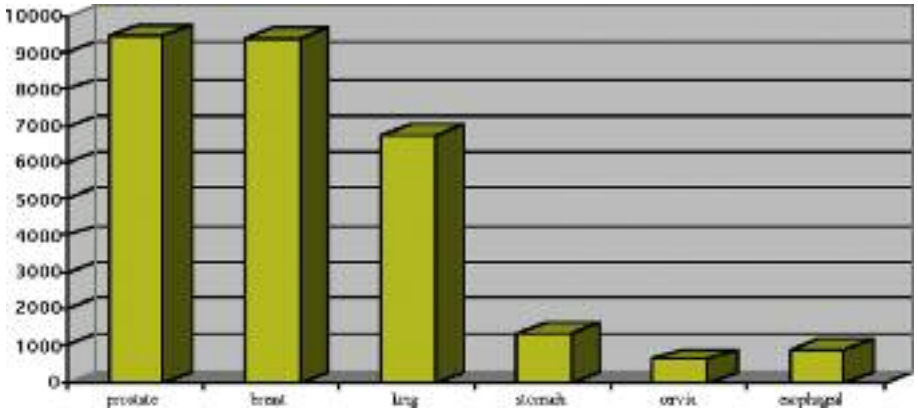
Serology can be useful in epidemiological studies or can be used if validated locally.

Confirmation of eradication is recommended. The first choice test for this is the ^{13}C-UBT (24). No comment is given concerning the cost-benefit of confirmation after eradication. Cost-effective analyses have been performed in complicated ulcers and showed a cost-benefit for confirmation (25). In other studies cost-benefit is less clear (26).

Treatment

Another change in the consensus concerns treatment. The **first line** classical triple therapy including clarithromycin, amoxicillin and a PPI, is now challenged by

Table 1. — **Incidence of several cancers in Belgium in 2005**



an increasing level of clarithromycin resistance that jeopardizes the treatment success. It is now recommended to extend standard triple therapy beyond 7 days or to adapt the treatment choice to the local resistance pattern. If resistance to clarithromycin is superior to 15-20% it is not advised to use clarithromycin. If the resistance to metronidazole is lower than 40%, it is advised to use metronidazole instead of amoxicillin. A 7 day treatment may be acceptable where local studies show that it is effective. Another option proposed by the consensus as first line therapy is the bismuth based quadruple therapy. No advise was given concerning the sequential therapy but only that it deserves further evaluation.

What about the sequential therapy ? This therapy consists of 5 days amoxicillin 1g bid and PPI bid, followed by 5 days metronidazole/tinidazole 500 mg, bid, clarithromycin 500 mg, bid, and PPI bid. In fist line therapy eradication rates exceed 90% in studies from Italy but in other countries results are between 50 and 90% (27,28, 29,30). These results are better then those of the classical triple therapy (PPI/amoxicillin/clarithromycin) and probably better than PPI/Metronidazole/clarithromycin 7 day therapy (no comparative studies) but are similar to a quadruple therapy (PPI, amoxicillin, clarithromycin and metronidazole) although results from these studies date from 2000 and older (31).

The scientific background for the sequential therapy is the following : amoxicillin prevents the development of efflux channels for clarithromycin by weakening the bacterial wall ; furthermore, by reducing bacterial burden before exposure to clarithromycin, the statistical risk of developing random mutations in the *H. pylori* 23S gene (the cause of resistance) is much less likely. The same can be said for metronidazole resistance where a random mutation inactivates the rdxA gene (32). The group of Zullo *et al*. also state that decreasing the bacterial burden increases the efficacy of the triple therapy PPI/metronidazole/clarithromycin (studies based on results of UBT tests for bacterial burden (27). However, when comparing eradication in patients with high or low UBT test, no difference is found between the two groups (33,34).

In Belgium, the information on antibiotic resistance is scarce (Table 2). Published data from 2002 from the Erasme hospital in Brussels showed 31% resistance to metronidazole and 3% resistance to clarithromycin (35). Results from the Queen Fabiola Children‘s Hospital from 1995 to 2000 showed metronidazole resistance to be rather constant around 18% while clarithromycin resistance increased from 6 to 16% (36). Data from 1997 to 2005 from a combination of several hospitals around Brussels, presented by V.Y. Miendje Deyi during the Belgian Week of Gastroenterology in 2008 and 2009, showed a large variation in the resistance to clarithromycin, in children as well as in adults, with resistance increasing to more than 25% in 2000 but decreasing again to an “acceptable” resistance rate of ± 12% in 2005 (37). Metronidazole-resistance fluctuated around 32% in adults. Our own preliminary results from a prospective study, also presented during the Belgian week 2009, confirmed these results (38). These results follow the trend in Western Europe (39).

This means that, if we apply the consensus, we should use first the combination clarithromycin/metronidazole. Concerning the duration of the treatment we can only observe that there are no recent studies available on the efficiency of the classical 7 day triple therapy in Belgium.

As a **second line** treatment bismuth based quadruple therapy stayed the fist choice but alternatives are PPI, metronidazole, ampicilline with still 64% eradication success even if resistance to metronidazole is present and the combination of PPI, tetracycline and metronidazole. Duration of therapy is not mentioned but used to be 14 days.

As bismuth is no longer available in Belgium, although it can be achieved through certain pharmacists, PPI would be used in stead of bismuth. Encouraging results exist for this combination in a first line treatment scheme with 91% eradication rates (40) but results are old and limited. To our knowledge, no studies exist using PPI instead of bismuth in combination with tetracycline

Table 2. — **Resistance *helicobacter pylori* in the adult Belgian population**

	Clarithromycin	Metronidazole	Levofloxacin	Reference
Aguemon 2002	3%	31%	–	35
Glupzcinsky 2003/4	–	–	17%	47
Miendje 2004-2007	15%	37%	16%	37
Riga, Sept 2008 (Glupzcinsky)	22%	–	28%	47
Mana 2008	14%	28%	26%	38

and metronidazole in the second line treatment of *H. pylori*.

Third choice treatment was advised to be based on susceptibility testing. However, culture has some disadvantages. Availability is limited, culture is difficult and infections with bacteria with different resistance pattern in one individual exists, in adults as well as in children (41,42,43) Furthermore there is a discrepancy between the in vivo and in vitro results of metronidazole. If culture is not available, good results can be achieved with a third line therapy without microbiological testing (44). PCR is a newer technique that can evaluate resistance for clarithromycin and ciprofloxacin in about 3 hours on a individual basis (45,46) The technique is easy but expensive.

New antibiotics such as levofloxacin, rifampicin or rifabutin can also be used in combination with amoxicillin and a PPI with good results, as is mentioned in the consensus but without further recommendations. Probiotics can be added to all of these regimens to improve compliance by decreasing adverse events.

Rifampicin is not reimbursed for this indication and rifabutin is not available in Belgium. Of course rifampycine could be used outside reimbursement but increased use could increase resistance against microbacteria, as mentioned in the consensus, so this should be considered only in exceptional cases.

Levofloxacin has been used in first, second and third line therapy with good results in first line but variable results in second and third line therapy. The main problem seems the resistance to quinolones that is acquired very quickly in all parts of the world. One study from Belgium (Yvoir) showed a 17% resistance, mainly primary resistance, in 2006. In 2009 this already increased to 26% (37,38,47).

Do we have others alternatives in difficult situations ? Is it useful to increase the PPI dose or add H_2-antagonists (48) ? It is known that there is an increased activity of antibiotics in less acid environment and increased concentrations of antibiotics in the stomach when pH is increased (49). Furthermore, PPI are metabolised differently in patients, depending on the CYP2C19 polymorphism. In high metabolisers pH will remain at lower levels (50). Two small studies examined the eradication rate depending on the pH. A significant better eradication rate was obtained in patients in whom the pH was high, independent of the bacterial susceptibility to clarithromycin (51,52). However, contradicting results were published so that a meta-analysis was published in 2006. This concluded that regardless of the PPI dose, high metabolisers achieved less good eradication rates than slow metabolisers. However, differences in eradication rates were only observed when omeprazole was used. This supports the conclusion that the other PPI's are less affected by the CYP2C19 polymorphism (53). As in the Caucasian population nearly everyone is a quick metaboliser, it would be logical to increase the dose of PPI if omeprazole is used .

However, the major causes of failure remain antibiotic resistance and problems of compliance.

In **conclusion** we can resume that ITP and unexplained iron deficiency anemia have been added to the major indications for eradication. Concerning the non-invasive diagnosis, UBT followed by monoclonal stool test are the first choices. When endoscopy is performed, rapid urease test has a good specificity and sensitivity. In the prevention of gastric cancer the most important factor is to eradicate before premalignant lesions are present. In Europe, a 7 day treatment with amoxicillin and clarithromycin is probably still a good choice and the combination metronidazole-clarithromycin perhaps better. However, more information should be available on resistance and results of eradication in the region were you work. The newly proposed sequential therapy seems very promising but should be further evaluated in other countries outside Italy. Quinolones can be used in the first and second line therapy but resistance is very rapidly acquired and should probably not be used without antibiogram. In Belgium, there are no recent studies concerning the efficacy of the classical triple therapy but resistance for clarithromycin is around 15%, allowing the continuation of the classical therapy.

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