APPROACH TO *HELICOBACTER PYLORI* INFECTION IN SPECIFIC AGE GROUPS

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Abstract

The *Helicobacter pylori* infection features a series of particular aspects, depending on patients' age. In children, some particular aspects should be mentioned – for instance, the prevalence of the infection, the low complication rate and the risk of malignization, the diagnostic and therapeutic schemes that must be adjusted based on age. For these reasons, some of the recommendations for adults cannot be applied in children. Concurrently, management difficulties also occur in elderly patients in terms of risk of complications, higher rate of antibiotic resistance, presence of comorbidities and often concomitant medication. The article overviews the clinical, diagnostic and therapeutic aspects of *H. pylori* infection management in children and elderly patients, respectively.

Keywords: *H. Pylori infection, treatment, pediatric, elderly.*

1. MANAGEMENT OF *HELICOBACTER PYLORI* INFECTION IN CHILDREN

The *Helicobacter pylori* infection is acquired most frequently during childhood, being associated with a low socio-economic status that includes poor sanitation, crowded living conditions and poor water supplies. Even if the estimated prevalence in children is around 70% in developing countries and about 40% in the United States, the global rate is now declining. [1-3]

In the intrafamilial model of transmission, *H. pylori* infected mothers and siblings play a key role. Some interesting researches focused on the effects of the infection in pregnancy and tranmission of bacteria to neonates. Recent studies suggested that the vaginal yeast is a reservoir of *H. pylori* which could play a role in transmitting the bacteria from mother to neonate. A possible correlation between *H. pylori* infection, impaired placental development and a higher risk to develop preeclampsia has been described. [4,5]

In pediatric age patients, the clinical picture of the *H. pylori* infection can be polymorphous: patients are often asymptomatic, and when the infection is clinically manifest, the patient most often reports the dyspeptic syndrome. In children, the dispeptic syndrome entails numerous differential diagnosis issues, such as: gastritis, peptic ulcer, gastroesophageal reflux disease, ingestion of foreign bodies, celiac disease, teenage pregnancy, intoxications, etc. [6,7] As a result, testing for *H. pylori* may be considered in children with the dyspeptic syndrome.

Gastric or duodenal ulcer is associated with *H. pylori*, but it is less frequent, complications occurring less often in pediatric patients than in adults. In addition, the risk of gastric neoplasia (including both non-Hodgkin lymphoma – MALT, and adenocarcinoma) is lower in children.

On the other hand, some possible causal relations between several pathological conditions and the *H. pylori* infection have been reported in children. In this context, studies on the relation between gastritis with *H. pylori* and recurrent abdominal pain registered controversial results. Although some studies report an improvement of symptoms following eradication therapy in

patients diagnosed with recurrent abdominal pain and *H. pylori* infection, the data of a recent double-blind controlled study did not confirm this observation. [8] Moreover, the updated guidelines of ESPGHAN/NASPGHAN recommend testing for *H. pylori* infection in children with functional abdominal pain. [9] Studies on adult patients suggest that *H. pylori* is a protective factor for the onset of the gastroesophageal reflux disease, but a research conducted on pediatric patients revealed a significantly higher prevalence of reflux esophagitis in children infected with *H. pylori*. [10] Recently, there have been reported several pediatric cases diagnosed with esophageal and gastric polyps associated with chronic *H. pylori* infection. [11]

Unconclusive results are also reported for the relation between the infection with *H. pylori* and constipation or delayed somatic development in children. Some studies have shown that decreasing appetite in children with *H. pylori* is associated with a low level of plasma ghrelin, that returns to normal after an eradication therapy. [12-14] The current guidelines recommend testing for *H. pylori* infection when investigating causes of short stature. [9]

Infection with *H. pylori* was also associated with extraintestinal manifestations, such as immune thrombocytopenic purpura. This observation resulted from a meta-analysis according to which, in patients with immune thrombocytopenic purpura, a significant increase in the number of platelets was found in more than 50% of cases in which the infection was successfully treated. [15]

As previously mentioned, testing recommendations for *H. pylori* infection in children are also partially different from those accepted in adults. In accordance with the updated ESPGHAN/NASPGHAN guidelines, the testing recommendations for identifying the bacteria in children are as follows [9]:

Testing for *H. pylori* may be taken into consideration in children with gastric and duodenal ulcer; a "test and treat" strategy is not recommended in pediatric population. At the same time, the guidelines recommend testing in children with functional abdominal pain, or as part of diagnostic workup in children with short stature. Regarding iron deficiency anemia (IDA), testing for *H. pylori* should be excluded from the initial investigation, however it may be taken into consideration in cases of refractory IDA. Concurrently, there is insufficient evidence for testing to be routinely recommended in children with upper respiratory tract infections, periodontal disease, food allergies, etc. [9]

The recommendations regarding the initial diagnosis of *H. pylori* infection in pediatric patients are largely similar to those applicable for adults, consisting in either histopathology (*H. pylori*–positive gastritis) plus at least one other positive biopsy-based test (rapid urease test, PCR or FISH), or a positive culture. The optimal number of biopsies has also been modified; at least 6 gastric biopsies should be obtained, as follows: 2 from the antrum, 2 from the corpus, for the histopathological evaluation applying the updated Sydney classification, other 2 samples from the antrum and corpus for culture, and at least 1 additional sample from the antrum for rapid-urease test or molecular-based assays. The difficulties are related to the acceptance of endoscopy. [16] Each diagnostic test for the identification of the (invasive or non-invasive) bacteria should be performed at least 2 weeks after stopping any proton pump inhibitor, and at least 4 weeks after discontinuing any antibiotic treatment. [9]

Regarding the non-invasive tests for identifying the infection with *H. pylori*, the urea breath test (^{13}C-UBT) is highly specific and sensitive in children over the age of 6. Experience in children under the age of 5 and particularly in nursing babies is relatively limited and requires additional validation. The *H. pylori* stool antigen test is also a reliable non-invasive test. In general, stool antigen testing for *H. pylori* in children and teenage patients is used more frequently than the urea breath test. Current guidelines recommend antibody-based tests (IgG, IgA) for *H. pylori* in serum, whole blood, urine, and saliva in a clinical setting. Non-invasive tests should not be used for the initial diagnosis of the infection; in selected cases, non-invasive tests may be considered when investigating the causes of chronic immune thrombocytopenic purpura. [9]

Up to now, the first line therapy consisted in a triple therapy for 7-14 days, using one of the

following associations: triple therapy with a proton pump inhibitor (PPI) +amoxicillin+ clarithromyin or an imidazole or bismuth salts+amoxicillin+an imidazole or sequential therapy. Nowadays, it is considered that antibiotic susceptibility should be obtained before treatment's initiation, and that the treatment should be tailored accordingly. If primary culture and susceptibility testing is not available, the recommended first line therapy is a high-dose PPI+ amoxicillin+ metronidazole for 14 days or a bismuth-based drug. The initial duration of the therapy (7-14 days) and the dose were prolonged to 14 days if PPI was increased up to 2.5 mg/ kg per day. [9] The sequential therapy seems to be effective in children infected with fully susceptible strains, but it has the disadvantage of exposing the child to three antibiotics. [9] Controlling the eradication of the infection shall be carried out preferably *via* non-invasive testing performed within 4 to 8 weeks after the eradication therapy, respectively *via* the urea breath test or stool antigen test, using the ELISA method with monoclonal antibodies. The pediatric practice includes several causes that lead to treatment failure: adverse reactions, low compliance and antibiotic resistance. Metronidazole and clarithromycin resistance were assessed *via* population studies, which suggested that clarithromycin resistance is higher in the strains obtained from children than in those obtained from adults. [17] In case of therapy failure, several options are available, like performing a second endoscopy and using a tailored treatment for 14 days or treating like a double resistance (with PPI+amoxicillin+ metronidazole for 14 days, with a high dose of amoxicillin or a bismuth-based substance); in teenagers, levofloxacin and tetracycline are an option. Previous recommendations on sequential therapy in case of therapeutic failure are no longer supported. [9]

There is ongoing research underway on adjuvant therapies and measures for both pediatric and adult patients. Current evidence does not support the idea of a routine addition of probiotics to antibacterial therapy for reducing the side effects or for improving the eradication rates. Furher studies are necessary, focused on specific probiotic strains. [18-20]

The discovery of a vaccine will constitute a genuine revolution in the management of infections with *H. pylori*. In this respect, Zeng *et al*. conducted a study geared towards assessing the effectiveness, safety and immunogenicity of an oral vaccine for *H. pylori*. The study tested vaccine's effectiveness on 4,446 children in China and reported a 71.8% efficacy, but research in this direction continues as, for the time being, there is no truly effective available vaccine. [21]

In this respect, prevention is considered of crucial importance. Breast-feeding is considered to have a protective effect against *H. pylori* and it should be maintained up to 2 years of age, according to WHO reccomendations. Improvements in sanitation and household hygienic practices, together with simple and effective measures like washing hands, preparing food in a proper manner and drinking water from safe sources are the most effective measures to decrease the infection rate in childhood. [1,22,23]

2. MANAGEMENT ASPECTS OF *HELICOBACTER PYLORI* INFECTION IN ELDERLY PEOPLE

While the prevalence of *H. pylori* in developing countries is higher in children, in the developed countries its prevalence increases with age, probably as a cohort effect of a previous generation exposed to precarious socio-economic conditions. [24]

The studies conducted over the last decade have reported a high prevalence of *H. pylori* infection in elderly individuals, particularly in institutionalized people, with a prevalence from 70% up to 85%. [25] However, a significant reduction in its prevalence was reported in people over the age of 85, [26-27] which could be explained by the presence of atrophic chronic gastritis in older age groups and by a large-scale use of antibiotic and antisecretory therapies. [27]

3. CLINICAL MANIFESTATIONS OF *HELICOBACTER PYLORI* INFECTION IN ELDERLY PEOPLE

Epidemiologic and clinical studies record an increase in both the prevalence and severity of

gastrointestinal diseases that come with age. [28] Moreover, interesting recently reported data suggests an association between *H. pylori* infection and certain extra-digestive disorders, including some particularly frequent in the elderly ones. For these reasons, testing and treating of the *H. pylori* infection must be considered as major goals in the clinical practice for elderly people. However, only few studies have been published to this date on this patient category. [26,27,29]

Atrophic chronic gastritis. Recent studies suggest that the atrophic modifications in the gastric mucosa are associated rather with *H. pylori* infection than with aging. Eradication of *H. pylori* infection in elderly patients with advanced atrophic gastritis led to a significant improvement of the mean histologic score in terms of intestinal inflammation, atrophy and metaplasia after a mean 2.5 years' monitoring period. [30]

As to the *gastroesophageal reflux disease*, certain studies reported that eradication of *H. pylori* could cause reflux disease and erosive esophagitis symptoms. On the other hand, the results of other research appear not to support the involvement of *H. pylori* in the pathogenesis of reflux diseases. Consequently, the relation between the *H. pylori* infection and the gastroesophageal reflux disease is far from being elucidated. [31-33]

Although epidemiologic studies indicate that the prevalence and incidence of *gastroduodenal ulcer* are constantly decreasing in the general population, literature data argues an increased rate of ulcer disease related complications and mortality among elderly patients, probably *via* a broad use of nonsteroidal anti-inflammatory drugs (NSAIDs). [34-37] Therefore, testing and treating of the *H. pylori* infection is recommended in elderly patients. Moreover, for patients with comorbidities or a history of peptic ulcer requiring long-term NSAIDS treatment, it is recommended that the *H. pylori* infection eradication treatment be started before the treatment with NSAIDs. [38,39]

Gastric cancer is rarely diagnosed in people under the age of 30. After this age, the incidence grows rapidly and constantly, reaching its highest rates in elderly persons. It is a proven fact that in hosts with a genetic predisposition, the infection with *H. pylori* induces a cascade of changes that could ultimately lead to the development of gastric neoplasia. [40]

Extra-digestive diseases

There is a long list of diseases associated to *H. pylori* infection, the common factor of their pathogenesis appearing to lie in the proinflammatory nature of *H. pylori*. [41, 42] We will focus only on the extra-digestive diseases of interest in the treatment of elderly patients or in those with a significant social impact.

The results of the studies investigating the relation between the presence of *H. pylori* infection and *coronary pathology* are inconsistent. While certain studies prove a significant correlation between ischemic cardiopathy and chronic infection with *H. pylori* [43,44], others, conducted on elderly patients, failed to identify any association between *H. pylori* and the coronary disease [45] or systemic atherosclerosis. [46]

There are studies which reported the involvement of *H. pylori* in the pathogenesis of mild cognitive impairment [47] and Alzheimer disease [48-49], but further research is necessary. Another pathological condition in which *H. pylori* infection is possibly involved is minimal hepatic encephalopathy in patients with liver cirrhosis. [50]

In addition, as in the case of children, the *H. pylori* infection might be involved in regulating appetite in the elderly ones *via* hormonal modulation (leptin and ghrelin), which can thus influence the regulation of body weight, hunger and satiety. [51,52] This is a new field of interest, requiring further research.

Iron deficiency is a frequent cause of anemia in elderly people. The results of several studies proved a causal relation between the *H. pylori* infection and *iron deficient anemia.* [53,54] The possibly involved pathogenic mechanisms are occult bleeding related to erosive chronic gastritis, decreased iron absorption related to chronic corporal gastritis associated with hypo- or achlorhydria and the bacterial overpopulation phenomenon.

Vitamin B12 deficiency is also particularly frequent in elderly ones, but it often goes unnoticed, as its clinical manifestations are often subtle. [55,56] There are multiple causes for

vitamin B12 deficiency, ranging from pernicious anemia, gastrectomy, the use of gastric anti-secretory medicine, all the way to infection with *H. pylori*. [57,58]

The recommendations regarding the initial diagnosis of Helicobacter pylori infection in elderly patients are those established under the Maastricht consensus reports, with a few observations. [59]

Invasive tests

When histology examination is selected for diagnosing an infection with *H. pylori* in elderly patients, multiple biopsy samples must be collected (at least 2 antral biopsies and other 2 from the gastric corpus), because the increased frequency and severity of atrophic gastritis in elderly ones can reduce the sensitivity of the test. As for the rapid urease test, it can detect the presence of *H. pylori* with a satisfactory sensitivity (90%). [60]

However, similarly to histological diagnosis (for the same considerations), the rapid urease test conducted on antral biopsies has a lower sensitivity in patients over the age 60, compared to younger patients. [61]

These findings suggest that, in the case of elderly people, it is recommended to get biopsies from both the antrum and the gastric corpus and (possibly) to run a second test, if the rapid urease test is negative. Moreover, it is mandatory to stop the anti-secretory medication at least 14 days prior to testing.

Non-invasive tests

The *urea breath test (UBT)* has a 95% diagnostic accuracy. [62] Studies conducted on patients over the age of 65 proved that the UBT test – in comparison with serology (*IgG anti-H. pylori antibodies*) – has much higher scores in terms of sensitivity (100% vs 74.4%), specificity (95.7% vs 59%) and diagnostic accuracy (98% vs 67%). [63-65]

The stool antigen test for detecting H. pylori is an accurate non-invasive method both for the initial diagnosis of the infection and for confirming its eradication after the treatment. [66]

However, in the case of elderly individuals, certain limitations can occur in this test because of constipation, which is frequent in this age group. Extended gastrointestinal transit times could lead to the degradation of *H. pylori* antigens and could compromise their detection. [27]

4. TREATMENT OF *HELICOBACTER PYLORI* INFECTION IN ELDERLY PEOPLE

Triple therapy (PPI, clarithromycin and amoxicillin or metronidazole) recommended by the Maastricht consensus was proved equally effective and safe for the treatment of *H. pylori* infection in elderly patients. In this case, quadruple regimens based on bismuth salts are also an alternative for primary-line treatment. Although it is widely accepted that the extension of treatment duration up to 10 or even 14 days is associated with a higher rate of eradication, in the elderly ones it appears that extending the duration of the treatment can increase the risk of side effects, which become more clinically significant after the first week of treatment. [67,68]

Several aspects need to be mentioned with regard to *H. pylori* eradication in elderly subjects.

Eradication of *H. pylori* infection is more difficult after a failed initial treatment attempt, the more so that the optimal strategy for re-treatment has not been yet determined for the elderly ones. [69]

Firstly, antibiotic resistance is very frequent in this patient category because of the need to use drug associations with therapeutic agents from various pharmaceutical classes – antibiotics included. [29,70] Special attention must be paid to levofloxacin resistance, which is increasingly reported primarily in patients with chronic respiratory pathology, often treated with fluoroquinolone. [59]

Secondly, drug interactions have to be considered as a particular issue in elderly people.

Although the type of PPI used in the schemes for eradicating *H. pylori* does not affect the success of the treatment when used in standard doses, some PPIs can have multiple drug interactions. Out of all PPIs, omeprazole is the most likely to produce drug interactions, especially with certain antiplatelet agents (clopidogrel) and other drugs used in cardiovascular pathology, both of these categories

of drugs being commonly used in elderly people. On the other hand, the lowest amount of interactions was reported for pantoprazole. [71]

Similarly, the antibiotics used for eradication – such as clarithromycin, amoxicillin, metronidazole and tetracycline – can interact with the medicine commonly used in elderly patients. [72] Although it is not easy to determine all effects of drug interactions, the therapeutic agents used in cardiology (statins, antiarrhythmic, warfarin) are among those having a well-established interaction with these antibiotics. [72] If the risk of interaction exceeds its benefit, any eradication treatment must be avoided or suspended.

Moreover, certain comorbidities in the elderly ones could require additional changes to the treatment scheme. For instance, while metronidazole can be used without adjusting the doses in patients with kidney failure, amoxicillin and clarithromycin require dose adjustment for patients with creatinine clearance below 30 ml/ min. At the same time, antibiotics can cause temporary and mildly elevated liver enzymes, but severe hepatotoxicity is unlikely, particularly during short-term use. PPI dose adjustment is not necessary for elderly patients or for those with mild kidney or liver failure. [72]

5. CONCLUSIONS

The diagnostic and treatment of *H. pylori* infection in children and elderly patients should be seen as major goals in clinical practice, considering its involvement in the pathogenesis of several gastrointestinal and extra-digestive diseases.

The current recommendations for diagnosing and treating *H. pylori* infection confirm that the standard methods implemented by the Maastricht consensus are safe and effective to a wide extent, regardless of age. Nevertheless, due to the particular age-related conditions, a multidimensional approach is mandatory, for both pediatric and elderly patients alike. Moreover, in order to optimally manage the situation, the elderly ones require an assessment of the functional, cognitive, and nutritional conditions, as well as of the comorbidities and concomitant treatments.

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