

# Gut

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## Leading article

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### *Helicobacter pylori* in eastern European countries: what is the current status?

A considerable interest in *Helicobacter pylori* infection and its consequences for humans has been seen since the beginning of the past decade in different countries all over the world.

In recent years this bacterium has also drawn attention from scientists in eastern Europe and has become the subject of numerous scientific investigations carried out in this part of Europe. It has become rapidly clear that *H pylori* infection is very common in eastern European populations and that *H pylori* associated diseases are responsible for a large part of the gastroduodenal disorders seen in Eastern countries. Moreover, the discovery of *H pylori* has shed new light on the aetiological factors responsible for the development of certain diseases commonly seen in Eastern countries, such as peptic ulcer disease and gastric cancer.

Although *H pylori* research in Eastern countries dates back to 1986 and 1987, it was only in October 1992 that the investigators from eastern Europe interested in *H pylori* were given the opportunity to meet together for the first time. The meeting, devoted to *H pylori* research and new trends in gastroduodenal disorders in Eastern countries, was organised in Prague by the European *Helicobacter Pylori* Study Group and permitted the exchange of experiences in the *H pylori* research field among about 100 scientists from Albania, Bielorrussia, Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Lithuania, Poland, Rumania, Russia, Slovakia, Slovenia, and Ukraine. The data presented at this meeting made many of the participants realise the importance of *H pylori* infection and its possible consequences for the Eastern communities.

#### Diagnosis

When evaluating the current status of *H pylori* research carried out in Eastern countries, it should be kept in mind the particular conditions, especially financial limitations, which exist in these countries and which make all the scientific investigations performed there more difficult than in the Western part of our continent.

As far as *H pylori* research is concerned, such limitations emerge first in choosing the appropriate methods for the diagnosis of this infection. Generally, the simplest and the least expensive methods are preferred for the detection of

*H pylori* infection. Thus, the techniques most commonly used are the rapid urease test and histopathological diagnosis after Giemsa staining, although culture is also used in some places. Urea breath test is almost never used in Eastern countries except for specific research purposes.

In a report by Bazhenov *et al* from Russia, the authors found the sensitivity and specificity of the urease test based on the standard ingredients made in this country to be similar to those of the commercial Jatrox-CLO-test.<sup>1</sup> Even if these tests are used at their optimal efficacy, however, they suffer from the lack of sensitivity linked to the test itself. This aspect must be considered when data derived from biopsy material are presented.

The most commonly used serological methods are enzyme linked immunosorbent assay (ELISA) and passive haemagglutination test, both usually based on home made antigens.

The study by Szentmihalyi *et al* from Hungary, comparing the efficacy of different diagnostic methods (culture, rapid urease test, and serology) in the detection of *H pylori* infection, illustrated a low sensitivity for the urease test and the necessity of using two or three different diagnostic methods to obtain reliable results.<sup>2</sup>

The efficacy of the different methods in the diagnosis of *H pylori* infection may be presented by comparing the rates of *H pylori* positivity found in the groups of patients with different gastroduodenal diseases. In patients with duodenal ulcer disease, the presence of *H pylori* infection ranged from 74 to 100%, depending on the detection method used.<sup>3-5</sup> In different reports on patients with gastric ulcer disease, 50 to 88% were infected with *H pylori*, while in patients with different types of chronic gastritis the infection rate ranged from 60 to 83%.<sup>3-9</sup> In one study by Preobrazenskij *et al*,<sup>10</sup> among 89 patients with longterm non-healing gastric ulcers, *H pylori* was detected in only 18 (19.8%) by CLO test, while some other abnormal gastric flora was found in 72% of these patients. These somewhat surprising results could be explained by the severe atrophy of the gastric mucosa present in these patients, accompanied by hypo or achlorhydria creating an unfavourable environment for *H pylori*, but at the same time favouring the overgrowth of other bacteria.

The frequency of *H pylori* infection in patients with stomach resection was found in one of the studies

performed in Rumania<sup>11</sup> to be 61·2% by rapid urease test, while the corresponding figure in Poland (author's unpublished data) was 66%.

### Epidemiology

The data resulting from the seroepidemiological studies show an extremely high prevalence of *H pylori* infection in the normal populations of eastern Europe. It is worthwhile pointing out that, unlike in Western countries, the infection begins at an early stage in life and increases rapidly with age reaching the level of 80 to 90% of infected subjects as early as the age of 20. In the Polish study,<sup>12</sup> 18% of children aged 0 to 4 years were already *H pylori* positive, while the average infection rate for adults aged 20 years and above was 87%. Similar results were obtained in Estonia,<sup>13</sup> where the age groups ranging from 15 to 19 years and 20 to 29 years presented an *H pylori* infection rate of 69% and 83%, respectively. In a study performed in Slovenia,<sup>14</sup> seropositivity to *H pylori* increased rapidly from 38% in subjects aged 0 to 29 years to 73·5% in those aged 30 to 39 years.

This pattern of age dependent *H pylori* acquisition resembles that seen in developing countries and is considerably different from that noted in western Europe.<sup>15</sup> While considering the possible factors responsible for this high infection rate, the poor socioeconomic conditions of most of the Eastern societies should be considered, especially the war and postwar generations of 1940 to 1960. According to the newest hypothesis on the epidemiology of *H pylori* infection, transmission usually takes place at an early stage of life, mainly in childhood. And indeed, this postulate is supported by the results of the Polish study,<sup>12</sup> where a considerable decrease in the prevalence of *H pylori* infection was seen for the subjects born after 1970, reflecting an improvement in the socioeconomic status of the Polish society that took place in the 1970s.

### Natural history

During recent years, follow up studies have been performed in Eastern countries to examine the natural history of *H pylori* infection and *H pylori* associated gastro-duodenal disease. Eastern countries seem to be an ideal place for such studies, in that *H pylori* infection is very common and most of the patients are cooperative and eager to submit themselves to several reexaminations over a long period of time.

One of these studies<sup>16</sup> was conducted to evaluate the frequency of the development of peptic ulcer disease in patients with chronic gastritis and with no previous history of peptic ulcer disease, according to their *H pylori* status at the beginning of the observation period. The study showed that, in patients with *H pylori* infection, there was a high probability of the development of peptic ulcer; during a five year long observation period, 21% of these patients developed gastric or duodenal ulcer. In contrast, in the *H pylori* negative patients, during the same period of observation, gastric ulcer was found in only one patient (3·4%). A comparatively high number of *H pylori* negative subjects were included in this study, which is surprising considering the high prevalence of this infection in the general Polish population. This may be explained by the criteria of recruitment of the patients in this study, which favoured subjects promising good cooperation over a long period of time, thus selecting people from a high socioeconomic group.

Another follow up study with 86 patients of an urban Estonian population was designed to assess the changes in the extent of *H pylori* colonisation and the grade of

gastritis during a six year long observation period. The study showed that appearance of *H pylori* colonisation was accompanied by an appearance of gastritis, and an increase in the extent of *H pylori* colonisation was followed by an increase in the severity of superficial gastritis. Moreover, the study showed that the gradual increase in the extent of *H pylori* colonisation paralleled the progression of atrophy in the gastric mucosa.<sup>17</sup>

### Peptic ulcer disease

As *H pylori* infection is strongly implicated as an aetiological factor in the development of peptic ulcer disease, the question arises of the possible impact of such a high *H pylori* infection rate seen in Eastern countries on the incidence of these diseases.

Unfortunately, reliable data on the peptic ulcer disease epidemiology in eastern European countries are lacking. The duodenal ulcer disease incidence in 1991 and 1992 was assessed, however, for one Polish city, Wroclaw (southwest Poland) with 700 000 inhabitants and was found to be considerably higher than the duodenal ulcer disease incidence evaluated in recent years (1980 to 1990) for different Western cities (3·3 v 0·6–0·8/1000 inhabitants of both sexes, aged 15 years and older, in Reims, France).<sup>18</sup> Although peptic ulcer disease incidence rates tend to be decreasing, in Poland it is still assessed that about 10% of the population will suffer from peptic ulcer disease at least once during their lifetime. The data available from Russia show that in the 1970s, peptic ulcer disease incidence varied in different regions from 5·2 to 12·2/1000 inhabitants, the highest (12·2) being in Siberia.<sup>19</sup>

### Gastric cancer

The data on the epidemiology of gastric cancer show that eastern Europe presents one of the highest gastric cancer incidence rates in the world. The age standardised death rate for stomach cancer for men from 1981 to 1986 was 26·0 in Poland, 24·4 in Hungary, and 20·9 in Czechoslovakia, while at the same time it ranged from 5·0 to 16·0 for different western European countries.<sup>20</sup>

The gastric cancer incidence rate for men in Poland varied from 29·3 to 42·8/100 000 inhabitants/year.<sup>21 22</sup>

### Paediatrics

Results of seroepidemiological studies in eastern Europe have shown that *H pylori* infection is common among children. The longterm consequences of *H pylori* infection are probably dependent on the age of acquiring the infection as well as on other factors, and are probably more serious (for example, higher predisposition to gastric cancer) when infection takes place early in life; therefore, *H pylori* detection in children seems to be of the greatest importance.

Numerous studies have been performed on children with abdominal complaints and *H pylori* infection was confirmed in 30 to 35% of those studied by means of various methods (urease test, histopathology using Giemsa stain, etc). In a study by Soucek *et al*, 132 (30%) of 451 children with dyspeptic symptoms were *H pylori* positive. Histopathological features of chronic gastritis were present in 92 (72%) of the *H pylori* infected children versus 61 (19%) of the non-infected children.<sup>23</sup> Maaros *et al* reported that 108 (61%) of 178 children, aged 4 to 15 years with abdominal complaints, presented with chronic gastritis and *H pylori* was found in 90% of them.<sup>24</sup>

Another study performed in Russia by Szczerbakov *et al* showed that among 137 children (aged 1 to 15 years) who had endoscopic examinations because of upper abdominal complaints, 45 children had duodenal ulcer, 55 gastro-duodenitis, and 34 gastritis only. *H pylori* infection (detected by urease test and Giemsa staining) was found in 100%, 83%, and 83% of these various groups, respectively.<sup>7</sup>

### Basic research

A strong interest in basic *H pylori* research also exists in Eastern countries. Among others, we would like to report two Czech studies: one study, by Korych *et al*, concerned the adherence of freshly isolated strains of *H pylori* to HeLa cells in culture and the morphological changes of these cells after infection.<sup>25</sup> The second, by Fixa *et al*, entailed the inhibition of leucocyte migration in *H pylori* positive patients, which confirms the development of a specific cellular immune response to *H pylori* in infected subjects.<sup>26</sup>

### Treatment

The question that emerges after the *H pylori* infection is finally diagnosed is what treatment should be applied. Amoxicillin, erythromycin, and metronidazole are among the most popular antimicrobial agents used in the treatment of *H pylori* infection in eastern Europe. While H<sub>2</sub> blockers and bismuth salts are the leaders among the antiulcer drugs given, omeprazole is practically never used because of its cost, with the exception of research purposes. Triple therapy with one antiulcer and two antimicrobial drugs is recommended if available. It should be remembered, however, that in some regions (for example, Albania) there is an extreme lack of any antiulcer and antimicrobial drugs, and in some other areas (Rumania, personal communication), only a narrow spectrum of medicine is available. Such limitations have a strong impact on the results of the treatment of peptic ulcer disease and some other gastroduodenal diseases and are probably responsible for the high rate of peptic ulcer disease complications seen in Albania.<sup>27</sup>

The efficacy of anti-*H pylori* treatment varies significantly depending on the therapeutical regimen used. Numerous clinical trials have been performed during recent years in eastern Europe to find not only the most efficient, but also the least expensive treatment of the *H pylori* associated gastroduodenal diseases. The results of one of these trials (author's unpublished data) comparing the anti-*H pylori* efficacy of two regimens: CBS (480 mg four times daily/28 days)+amoxicillin (1.5 g thrice daily/10 days)+metronidazole 1.5 g thrice daily/10 days) versus ranitidine (300 mg twice daily/28 days)+amoxicillin+metronidazole (same doses as above) showed that both regimens were equally effective in eradicating *H pylori* (61.5% and 62.5% eradication, respectively).

Another clinical trial was performed in Bratislava (Slovakia) to assess the efficacy of anti-*H pylori* treatment in 230 patients with non-ulcer dyspepsia. Double therapy comprised of bismuth subnitrate (240 mg thrice daily/20 days) and metronidazole (250 mg twice daily/14 days) resulted in a 53% eradication rate. Disappearance of dyspeptic symptoms occurred in 73% of the patients in whom bacteria were eradicated and in 41% of those in whom eradication was not achieved.<sup>28</sup>

The study by Szczerbakov *et al* clearly showed the superiority of double therapy to monotherapy in the treatment of *H pylori* infection in children (89% eradication by CBS versus 100% by CBS+tinidazole).<sup>7</sup>

The results of a study by Grigoriev *et al* in Moscow showed that eradication of *H pylori* in patients with peptic ulcer disease may change the natural history of this disease. Findings over 12 months showed that, in duodenal ulcer disease subjects in whom *H pylori* was eradicated, the relapse rate of peptic ulcer was significantly reduced compared with *H pylori* positive subjects in whom eradication was not achieved (cumulative relapse rate in the two groups was 2 versus 12, respectively).<sup>29</sup> As *H pylori* infection is acquired mainly during childhood and the probability of becoming infected in adulthood is low, the probability of reinfection in patients in whom *H pylori* was successfully eradicated is negligible, giving a good prognosis for the course of the ulcer disease in the future.

There are several reports in Eastern countries describing the failure of *H pylori* eradication caused by the metronidazole resistance of some strains. In one report from Bulgaria, 37% of *H pylori* strains were metronidazole resistant, while the author's unpublished findings indicate the presence of only 20% of such strains in the patients examined in Poland.<sup>30</sup>

In summary, *H pylori* infection in Eastern countries is very common and is accompanied by a high incidence of peptic ulcer disease and gastric cancer. Despite many structural difficulties, there is an increasing interest in *H pylori* research in this part of Europe and results of numerous recent studies have shown a strong causative relation between *H pylori* infection and the development of some gastroduodenal diseases in Eastern countries.

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