

Helicobacter pylori infection: extragastric effects and diseases (critical analysis)

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With the discovery of Helicobacter pylori (HP) [41] appeared in gastroenterology powerful incentive to study the role of infectious factors in the development of various gastroduodenal diseases, because, as it turned out, the ecological niche for HP is exactly the gastric mucosa, especially its piloroantralno department. Some authors have even started to talk about the infectious "renaissance" [4, 5], ie about reviving attempts to link the origin of a number of idiopathic (of unknown cause) diseases with a bacterial infection, bearing in mind primarily the HP.

Over the past 30-odd years after the opening of HP tremendous amount of research has been published that have examined various aspects of HP-infection: their microbiological characteristics, molecular-biological basis of variability, virulence factors (pathogens), epidemiology, modes of transmission and clinical forms of HP-associated diseases. For example, HP has been studied role in the etiology of certain forms of chronic gastritis (CG), the pathogenesis of peptic ulcer (PU), the development of MALT-lymphoma, low-grade and distal gastric cancer (GC).

This flurry of publications and excessive interest to gastroenterologists HP-infection as a pathogenic factor involved in the development of a number of common gastrointestinal diseases, can be explained by the lack of major advances and discoveries in the preceding period of Gastroenterology.

Epidemiological studies have found that HP-infection is widespread among the population all over the world: up to 60% of the total population are infected with HP since childhood. However, as it turned out. HP does not have invasiveness and in most cases (about 70%) during the whole life do not cause him any pathological processes. IE Tkachenko (1999), to emphasize the low virulence of the HP, offered to call them "therapeutic infection" (in contrast to the highly virulent "surgical infections") [13]. It was a reasonable proposition that HP — it commensals ("fellow diners"), which are an integral part of human normobiotsenoza and purchase some strains of HP virulent (cytotoxic) properties — the result of any mutation resulting irrational antibiotic therapy and, therefore, has the iatrogenic origin [13, 19, 20, 24, 25, 26].

In this article, we do not set the task to discuss the role of HP infection in the etiology and/or pathogenesis of HP-associated gastroduodenal diseases — these questions will be fully addressed in previous publications [15, 16, 17, 18, 19, 20, 21].

Our aim is to establish the validity of the current tendency to the claim if the HP-infection plays a role in the development of various vnezheludochnyh diseases, including idiopathic (gastrointestinal, cardiovascular, etc.).

Because HP regarded until recently as a non-invasive microbe with mild expressed virulent properties, which is capable, under certain conditions cause pathological processes only in places of their habitat (stomach, rarely duodenum (KDP), on condition that it centers of gastric metaplasia), the possibility of development of HP-related diseases in other organs of the digestive system and even

more so in other systems and organs require a thorough discussion from the perspective of evidence-based medicine.

Previously, as already indicated, conclusive studies it was found that HP — noninvasive microbe capable colonize only columnar epithelium of the gastric mucosa, but it can't exist and reproduce any intestinal columnar epithelium or on a multilayer planar non-keratinizing esophageal epithelium. Nevertheless, in the domestic medical journals started to appear in the publication, which is asserted that HP, including their cytotoxic (CagA-positive) strains freely circulate in blood (bacteremia) and form microbial colonies on the squamous epithelium of the esophagus [2, 12]. Because this data is fundamentally contrary to the previously established facts, careful verification of their evidence, including the specificity and sensitivity of the methods employed. In this connection it is appropriate to recall that Article J. Warren and B. Marshall (1983) on the HP of the opening was not published «Lancet» editorial staff as long as the data submitted by them were not confirmed (rechecked) in other research laboratories [41].

Just in case, if it is definitely proved that HP — an invasive microbe persistent in the human bloodstream, it can cause the formation of metastatic lesions in other organs and tissues, can seriously discuss the possibility of HP-associated non-gasytic diseases, study of cause effect relationships between them, recognize HP direct or indirect role in their emergence and development.

For example, several attempts to associate with the HP-infection development of several hepatobiliary diseases. However, conclusive research CA Fallone et al. (2003) found that when cholelithiasis, sclerosing cholangitis and primary cancer pancreobiliary bile obtained during endoscopic retrograde cholangiopancreatography, HP, are generally absent. The authors used for gene identification HP-specific primers capable of detecting in 1 ml bile from 100 to 1000 microorganisms. In 122 of the 125 patients with hepatobiliary pathology bile was HP-negative (PCR results) [32]. These data cast doubt on the possible link between HP-infection and the development of these diseases.

The question arises, how the HP 3 cases still might be in the bile? It is known that the main mode of HP infection is fecal-oral [5]. In unfavorable conditions for their existence are transformed HP from spiraling into coccoid form that serves as a way for their survival as a species of microbes in the case of displacement of their ecological niche in the gastric mucosa. This will ensure their safety in the intestines and excretion into the environment (soil, water, and so on. N.). Interesting fact: PCR fragments of HP antigens in the intestine were found in South American mummies (in Colombia), whose age is estimated at 1700 years [34]. Perhaps, in exceptional cases, HP coccoid forms may be retrograde (ascending path) to penetrate from the duodenum to the gallbladder. But it can't serve as proof of HP's ability to adhesion and the formation of microbial colonies in the epithelium of the gallbladder, their causal role in the development of biliary pathology. There is the notion of "simple bakterioholii" when microbes penetrated into the gallbladder, pass through it in transit and are excreted with the bile into the duodenum.

Because bile were identified not HP, a *Helicobacter bilis* (spindle-shaped gram negative microbe in a mobile stick). However, it failed to prove its etiological role in the pathology of the gallbladder and extrahepatic bile ducts, in the development of

specific diseases of the hepatobiliary system. Furthermore, *Helicobacter bilis* They were identified only in animals (dogs, cats, mice, rats), but not in humans [1, 31].

It was also suggested that HP-infection of the gastric mucosa in cirrhosis ammonium can improve serum levels [30]. However, conclusive studies failed to confirm the differences in ammonia content in blood at the initial (sub-clinical) stages of hepatic encephalopathy complicating cirrhosis, in HP positive and HP-negative patients [33, 40].

Hypothetical HP-infection connection with pancreatic diseases based on their putative role in the development of biliary pathology (which is not confirmed), it is known the existence of chronic biliary pancreatitis [7]. The study's author is forced to admit that the specific mechanisms HP relationship with diseases of the pancreas unknown to science. As evidence of the role in the development of HP pancreatic diseases it refers to the detection of antibody (IgG) to HP in the serum of these patients. However, given the widespread availability of HP in a population of serum anti-HP antibodies in patients with pathology of the pancreas only indicates persistence of these bacteria in the human stomach, but can't demonstrate their role in the development of pancreatic diseases. In addition, 60% of the patients were simultaneously diagnosed with HP-associated duodenal ulcer. The author said publication even tried to identify specific strains of HP, primarily affecting the pancreas, but, as might be expected, he did not succeed, how can't detect ulcerative and carcinogenic strains of HP, because they do not exist in nature [3]; no pancreatogenic HP strains.

In a few publications reported, though HP (their VacA-positive strains containing vacuolating cytotoxin) inhibit the exocrine function of the pancreas [35]. But even if these findings are confirmed, they can't HP serve as proof of direct involvement in the development of diseases of the pancreas. There is no doubt in the existence of a close connection between all bodies gastroduodenocholangiopancreatic system (complex), so in the development of any HP-associated gastroduodenal diseases (chronic hepatitis, ulcer, gastric cancer and OE) in one way or another will inevitably violate the functions of all or most of the organs of the system, including pancreas, with common mechanisms of regulation and constant interaction in the processes of digestion.

In chronic inflammatory bowel disease in 60.9% of cases identified in HP-infection of the gastric mucosa. This was the basis for the search for the relationship between HP and chronic inflammatory bowel diseases, in particular the formation of such patients gastroduodenal erosions [8]. It was found that patients with ulcerative colitis and Crohn's disease HP infection occurs significantly less frequently than in the general population and in the control group (60.9, 82.5 and 100%, respectively), and epithelialization detected gastroduodenal erosions have not It depends on the successful eradication of the HP, so eradication therapy to eliminate erosion in the lining of the stomach and duodenum in these patients is not practical, and any pathogenetic link between HP-infection, ulcerative colitis and Crohn's disease is not [8, 36].

There is even less justification for the assumption that there is a direct or indirect connection between the HP-infection and cardiovascular disease, especially atherosclerosis and coronary heart disease (CHD). Some authors refer to the frequency

of detection of antibodies to HP in this category of patients. However, a meta-analysis of 18 epidemiological evidence studies, involving more than 10 thousand. CHD patients have not confirmed the existence of links between the HP colonization of the gastric mucosa and the development of coronary heart disease [28]. It should be noted that so far not shown any research with epidemiological evidence of infection with HP-CHD correlation [5]. Using PCR fragments HP antigens also never been detected in atheromatous plaques [29], and the eradication of HP did not affect the level of fibrinogen and acute-phase proteins in serum of these patients [27]. Only one study [38] HP data communication and CHD were obtained. However, in-depth analysis based on various risk factors (social status of patients, body mass index, etc.). This relationship was not significant. TE Strandberg et al. (1997) on cross-analysis of data 624 patients with coronary artery disease in different ways Evidence-Based Medicine found no significant correlation between seropositivity for HP and cardiovascular disease. Their findings showed no clear link between the presence of HP-infection and coronary artery disease [39]. A. Khurshid et al. (1998) conducted a coronary angiography in 179 patients with clinical signs of coronary artery disease. At the same time the presence of HP was determined by serological methods (ELISA). Symptoms of coronary artery lesions were found in 68% of patients. There are no differences in the frequency of coronary heart disease in HP-positive and HP-negative patients have not been established ($r=0.63$) [37]. After controlling for other known risk factors, the relative risk of coronary atherosclerosis in the presence and absence of HP was 0.45 and 0.48, respectively ($p > 0.1$). Thus, HP-infection does not increase the risk of coronary heart disease and does not affect the severity of the atherosclerotic lesions of the coronary vessels. The authors concluded that HP is not an independent risk factor for atherosclerosis of the coronary arteries, and from the study data do not support HP value in the development of CHD.

Analyzing the causes of erroneous conclusions about the existence of the individual authors of a correlation between the frequency of detection of antibodies to HP and the presence of coronary artery disease risk factors, J. Danesh and R. Peto (1998) explain them either coincidence or publishing only positive results [4].

HP-infection assumption were made due to allergic diseases (asthma, angioedema, chronic recurrent urticaria, etc.), The development of which, however, was possible only in the presence of contributing factors, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), protozoan and worm infestation, dysbiosis (dysbiosis) bowel [23]. Discussing proposed mechanisms of allergic diseases in the presence of HP-infection, put forward three versions: 1) HP interact with mast cells, triggering the release of neurotransmitters; 2) HP, serving as a full-antigens, cause allergic reactions in the human body; 3) the HP reduce the barrier function of the intestine, causing (in incomplete hydrolysis of nutrient) intake of allergens in the blood [6].

Meanwhile, the presence of ulcerative colitis, Crohn's disease, helminths or protozoan infestations, as well as intestinal dysbiosis its barrier function is impaired regardless of the presence or absence of HP in the gastric mucosa. As the penetration into the human body of any foreign agent possessing antigenic properties with HP infection, the sensitivity of microorganism, and there is the possibility of allergic

reactions. However, we can't ignore that in the human body, particularly in the gastrointestinal tract, in addition to the HP, home to hundreds of species of microorganisms, including opportunistic, some of which have invasiveness. Therefore, there are sufficient grounds to link the occurrence of allergic reactions and diseases with the persistence of HP in the gastric mucosa. Link to a specific clinical benefit rate of eradication (HP) therapy in patients with diseases of the allergic nature (chronic recurrent urticaria, angioedema, asthma, etc.), In particular the possibility of dose reduction or even abolition of antihistamines and hormone drugs, can't serve as proof role in their development HP-infection as antibiotics used for HP eradication (clarithromycin, amoxicillin and al.), have a broad spectrum of antibacterial activity and inhibit vital functions not only HP, but many other organisms (obligate, opportunistic and pathogenic), including invasive properties which can cause allergic reactions and diseases.

Thus, attempts to connect to the HP infection the development of various non-gastric diseases, including listed as idiopathic group, were generally inconsistent and lacking in evidence.

In conclusion, we present the results of our research M-microflora, colonizing the stomach and duodenum (in addition to HP), in patients with duodenal ulcer. These data may have some value for a critical analysis of the topic.

Recent studies have shown that in healthy people in the antral mucosa and (rarely) fundus of the stomach in addition to the contamination of their HP (44.4 and 33.3%, respectively) can be detected and other microflora: streptococci (44,5-55,6% of cases), Staphylococcus aureus (61.1%), lactobacilli (44,4-50,0%), fungi of the genus Candida (22,2-27,7%) and others. [22]. Thus detect HP in an amount of 5.25 lg CFU/g Streptococcus — lg 4 CFU/g, staphylococci — 3.7 lg CFU/g lactobacilli — 3.15 lg cfu/g. There are a small number of other microorganisms: bacteroides, enterobacteria and korine-, micrococci. Apparently, not only HP, but other bacteria are able to adapt to the existence of a strongly acidic environment of the stomach.

Moreover, they can colonize the gastric mucosa in the form of a monoculture, and combinations of two or more cultures. Only 10% of healthy individuals was sterile gastric mucosa [22].

The microbial flora of the stomach may have a double origin: from the mouth and throat (oral-respiratory route) and from the intestines (fecal upward path).

With HCG, AJ and PU composition of the microflora, colonizing the gastric mucosa, more diverse, and its number increases substantially [22].

The latest recommendations of MK-4 (2011), dedicated to the diagnosis and treatment of the HP — associated diseases, noted: "As long as enough evidence linking HP-infection with different non-gastric diseases, including cardiovascular and neurological" [14].

Thus, the deep-rooted belief that only HP due to their inherent adaptive mechanisms capable of contamination of the gastric mucosa, is not confirmed. With comprehensive microbiological investigation failed to prove that identified in the mucosal layer of the stomach lining microflora is not transient, not accidentally entered when taking biopsies; This M-microflora, intimately related (adhesion) with epithelial cover. It is found that microorganisms colonize the gastric mucosa are specific antigens

(K antigens), which in certain circumstances can cause pathological changes in the gastric mucosa or exacerbation of preexisting disease (chronic hepatitis, PU).

According to our data [10], with M-duodenal ulcer microflora is most often detected in the inflammatory roller surrounding ulcerative defect in the duodenum. Microbial landscape periulcerous zone represented genera bacteria Streptococcus, Lactobacillus, Staphylococcus, Sarcina, Pseudomonas, Serratia, Actinomyces, and their number is 6 lg CFU/g (in healthy — less than 4 lg CFU/g), with a significant proportion of cases sown combination 3 -4 cultures. At the same unaltered portions of the mucous membrane of the stomach and duodenum are sterile. HP have been isolated from duodenal periulcerous zone only 12.5% of the cases [22].

The question arises: why, until recently, attracted the attention of researchers is not M-microflora of the stomach lining and duodenum, has not been studied its possible role in the pathogenesis of ulcer and its relapses along with HP-infection? This is partly explained by the enthusiasm of researchers click HP, and also the complexity of the bacteriological study of biopsies for the presence of M-microflora. For qualitative bacteriological analysis of biopsy should be thoroughly wash a 5-fold is replaced by 0.85% sterile sodium chloride solution, sterile homogenized in a porcelain mortar, dilute sterile meat-broth. After that the crop on nutrient media: liquid (meat-broth or medium Kitty Taronpi), thick (plain agar, blood agar, Endo medium Chistovich, Saburo or Kvasnikova).

In a study of 30 patients with duodenal ulcer recurrence in the phase we conducted a biopsy of the mucous membrane duodenal bulb from the zone of perifocal inflammation cytology smears and histological study of the biopsy. Determines the degree of microbial contamination of mucous membrane of the KDP in accordance with the visual analog scale morphological changes. After obtaining biopsy using sterile forceps endoscope was placed in a sterile tube with diabetes meat-peptone broth (0.5 ml), followed by classifying to a conventional agar. Bacteriological examination of biopsy performed by the usual method. Periulcerous degree of inflammation was assessed visually (in points): I degree — inflammatory roll less than 5 mm, II degree — 5-10 mm, III degree — more than 10 mm.

Antimicrobial therapy began with a 5-7 day. Upon detection of HP in biopsies prescribed standard triple eradication therapy (group 1); the detection of M-microflora carried differentiated antimicrobial therapy, taking into account the sensitivity of the selected microorganisms to antibiotics (group 2). The course of antimicrobial therapy in both groups was 10 days. After 4 weeks the control study was performed.

In patients with duodenal ulcer recurrence in phase I periulcerous degree of inflammation is defined in 36.6% of cases. Grade II — in 13.3% and grade III — in 51.1%. Colonization perifocal zone bulb DPK M microflora was found in $56,7 \pm 9,1\%$ of patients and in $64,7 \pm 11,5\%$ of cases prevailed of Streptococcus haemolyticus, to $9,2\% \pm 17,7$ — of Streptococcus viridans, in $3,6\% \pm 5,8$ — Escherichia coli, in $11,8 \pm 6,8\%$ — fungi of the genus Candida. HP found in $76,7 \pm 7,7\%$ of patients, including grade I-contamination was detected in $39,2 \pm 10,2\%$ of patients, II of the degree — at $47,8 \pm 10,4\%$ and grade III — at $13,0 \pm 7,1\%$.

Antibiotic therapy upon detection of M-microflora conducted sighting transcendoscopic method or prescribed antibiotics inside. In identifying the most

effective hemolytic streptococci were oxacillin and gentamicin, viridans streptococci — cephalothin and lincomycin, E. coli — kanamycin and gentamicin.

It is important to note that M-microflora isolated from periulcerous zone in patients with duodenal ulcer relapse is usually more virulent than HP, and has often invasive.

There was a clear link between the colonization of mucosal duodenal bulb M microflora and periulcerous severity of inflammation ($r=0.9$). After 4 weeks after a course of antibiotic therapy in both groups of clinical and anatomical remission was achieved [10].

Thus, according to our information, the effectiveness of differentiated antibiotic therapy aimed at eradication of M-microflora in patients with duodenal ulcer recurrence in the phase effect is not inferior to the standard three-circuit HP eradication. This suggests the possibility of participation M-microflora in the pathogenesis of recurrent duodenal ulcer, along with HP. Similar results were obtained group of clinicians and microbiologists (from the Institute of Epidemiology and Microbiology. Gamaleya, Moscow), which are published in a few years ago published a monograph [22].

In the introduction to the monograph mentioned known microbiologist A. Alexander Vorobyov said: "In recent years, actively discussed HP's leading role in the etiology and pathogenesis of peptic ulcer disease, chronic gastritis, esophagitis; developed and implemented in practice dozens of HP eradication schemes, involving a combination of different antimicrobials, often causing the development of dysbiosis and candidiasis. This circumstance is largely due to the fact that the developers of Helicobacter theory of disease was isolated from the whole M-zone microflora esophagogastroduodenal only HP and do not take into account the value of other representatives microbiocenosis".

And further: "The dominant place in the stomach and duodenum microbiocenosis take staphylococci, streptococci, micrococci, lactobacilli, fungi of the genus Candida and less — HP. Not gelikobakterioza and dysbiosis, characterized by excessive growth of M-microflora. is an important factor contributing to the activation of inflammatory and erosive and ulcerative lesions esophagogastroduodenal zone and used in eradication schemes antibacterial agents act on the entire M-flora, and not only on HP. "

In connection with attempts to extend the role of HP-infection for various idiopathic disease is appropriate to recall the words of the wise clinician EM Taresva: "Infectious concept is a permanent magnet, which distracts the attention of doctors and scientists from major non-infectious agent" [11].

Studies on the presence (in addition to HP) M-microflora, colonizing the stomach and duodenum in some healthy individuals and in patients with duodenal ulcer, suggest that the problem of HP-associated gastroduodenal diseases, including ulcer, is more complex than it appeared to recently, and is still far from a final decision [10, 9]. Further cooperation is needed gastroenterologists, pathophysiology, microbiology, immunology to study the role of infectious factors in the pathogenesis of PU. Simple solutions are not always characterized by reliability...

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***Helicobacter pylori* infection: extragastric effects and diseases (critical analysis)**

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Key words: *Helicobacter pylori*, lesion of gastroduodenal zone, cardiovascular disease, biliary pathology, M-microflora

Article contains review of the current literature with a critical assessment and author's analysis of the possible relationship between not only diseases of gastroduodenal zone, but of biliary tract, liver, pancreas, cardiovascular system,

allergic diseases and *Helicobacter pylori* infection. The author cites the results of their own research and considers it necessary to conduct further studies.