# The state of dysbiotic changes of the intestine and the level of system endotoxinemia in children with chronic gastroduodenal pathology

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**Key words:** children, chronic gastroduodenal pathology, Helicobacter pylori, microflora, endotoxin

## Introduction

The history of the study of the gastrointestinal microflora began in 1681, when the Dutch researcher Antoni van Leeuwenhoek reported his observations regarding bacteria and other microorganisms that were found in human feces. He advanced the hypothesis of co-existence of different types of bacteria in the digestive tract. The studies of the intestinal microflora composition, its normal and pathological physiology, and development of methods of positive influence on the intestinal microflora were started over 300 years ago and continue to the present time [7]. Eubiosis is evolutionary phylogenetically determined set of microbial communities colonizing the gastrointestinal tract of a healthy person. They are characterized by a specific qualitative and quantitative composition in different biotopes and are able to maintain necessary for human health biochemical, metabolic and immune balance [11]. Gastrointestinal eubiosis of a healthy person is differed by relative constancy and persistence of dynamic balance between the macroorganism and the association of microorganisms colonizing his digestive tract. The normal size and composition of microflora and its functional activity in different parts of the digestive tract may be only in the normal physiological state of the organism [1, 8]. On the one side, the violation of the qualitative and quantitative composition of the intestinal microbiota is associated with an increased risk of developing various diseases of internal organs. Recent studies indicate that microecological imbalance in the digestive system complicates the course of the disease, contributes to chronic course of pathological process and reduces the effectiveness of therapy. The intestine colonization by various pathogenic microorganisms contributes to structural changes in the mucous

membrane of intestine, reduces local immunity and initiates the development of inflammation. On the other side, the presence of chronic diseases, especially gastrointestinal pathology leads to the onset and progression of intestinal dysbiosis by the endotoxins effect, violations of adaptation and immunological mechanisms of protection [4, 12].

There is a point of view that the long-term existence of Helicobacter pylori (Hp) infection in the patient's organism, using of antibacterial drugs for the eradication of the bacterium can lead to development of secondary immunodeficiency. It is accompanied by the development of dysbiosis not only of the stomach and intestine with oppression of obligate and progressive growth of opportunistic and pathogenic flora, but also the entire gastrointestinal tract. The starting point in the development of this process is the oppression of indigenous anaerobic microbial component, which is in autoregulation and constrains the size of the population of potentially pathogenic microorganisms. So part of the normal flora in the activity system of colonization resistance cannot be questioned, and the violation of its quantitative and qualitative composition is considered one of pathogenetic formation mechanisms of chronic gastroduodenal pathology (CGDP) [2]. Dysbiotic changes in the intestinal microflora can be regarded in their turn as one of the causes of the development of Hp resistance to antibiotics conventionally used in the anti-Hp treatment schemes. These changes contribute to progressive decrease in the effectiveness of eradication of the microorganism [9].

By reducing of the barrier function of the gastrointestinal mucosa, due to inflammatory, destructive changes and dysbiotic changes, translocation of microorganisms to non-typical biotopes is possible. These changes may contribute the reducing of colonization resistance of individual biotopes, as well as the whole microecological system at all [13]. While the colon microflora performs multiple beneficial functions in healthy humans, bacterial overgrowth in the small intestine, especially in its proximal part almost always has negative consequences.

The basis of small intestinal bacterial overgrowth (SIBO) is the translocation of conditionally pathogenic flora in the proximal parts of the small intestine from other

biotopes, mainly the colon. It is diagnosed when the number of microorganisms in the small bowel exceeds $10^4$ colony forming units in 1 ml of aspirate [3, 13].

It is known that gram-negative microflora of the gastrointestinal tract is the source of endotoxin. Disruptions of the normal microflora correlation in the different parts of the intestinal tube may involve the accumulation of endotoxins of gram-negative bacteria in the intestinal lumen and their subsequent absorption, entering the systemic blood flow and the development of syndrome of chronic endogenous intoxication. Endotoxins are the lipopolysaccharides (LPS) of gram-negative bacteria, being a potent toxic factor and playing an important role in the immune regulation and maintenance of chronic inflammation [10]. LPS perform adaptive function in minimal concentration in the blood serum, whereas a higher level leads to the development of various inflammatory reactions.

In recent years an important role in the development and recurrence of erosive and ulcerative lesions of the gastric and duodenal mucosa is given changes microecology of the digestive tract against the persistent Hp [5, 6]. However, these works relate only to the adult patient population, and are mostly microbiological in nature. Studies that examine the influence of microflora on the course of CGDP in children are single, what makes a special interest in the matter.

**Aim of research** is to study the state of the intestinal dysbiotic changes and the level of systemic bacterial endotoxemia in children depending on the severity of CGDP.

**Materials and methods**

On the basis of the Donetsk city children's clinical hospital № 1 and Medical centre «Gastro-line», 280 children aged from 9 to 17, all with CGDP, were examined.

At the first stage of the study all patients were divided into four comparison groups: group I — 50 children with chronic gastroduodenitis (CGD), not associated with Hp (Hp-); group II — 50 children with CGD, associated with Hp (Hp+); group III — 60 children with duodenal peptic ulcer disease (DPUD), group IV — 120 children with erosive bulbitis (EB). In patients of groups III and IV destructive

changes in the duodenum were associated with Hp infection. The control group consisted of 30 conditionally healthy children without CGDP.

In order to confirm the diagnosis, all the children underwent gastric and duodenal endoscopy with a biopsy of the mucosa. Hp diagnostics was carried out by two methods: invasive — the rapid urease test with biopsy material, and non-invasive — the urea breath test using the test system «Helic» with detector tubes («AMA», Russia). Hp infection was determined in case of positive results of both diagnostic methods.

SIBO diagnostic assessment was performed for all children by the hydrogen breath test with lactulose load, using a digital analyzer of the exhaled hydrogen «LactofaH2» («AMA», Russia). Microbiological examination of feces was carried out according to the standard technique.

Investigation of systemic bacterial endotoxinemia was performed at the second stage of the study in 60 children with erosive and ulcerative changes in the duodenum (20 patients with DPUD and 40 children with EB). The control group consisted of 20 conditionally healthy children.

LPS concentration in the blood serum was determined by LAL-test «E-toxate» («SIGMA», USA), adapted to the clinical conditions and based on the endotoxin ability to cause coagulation of lysate protein fractions of crab hemolymph Limulus polyphemus, EU/ml.

Statistical analysis was performed in the package MedStat.

**Results and discussion**

Upon the hydrogen breath test with lactulose load, it was established that in children CGDP is combined with the development of SIBO. The overgrowth of fecal flora in the lumen of the small intestine in patients with CGDP associated with Hp, reveals significantly more frequently ($p<0.01$) relative to children without infection Hp. Thus, SIBO was diagnosed in 57 (95.0±4.9%) patients with DPUD. It was significantly higher ($p<0.01$) in comparison with children of groups I and II. SIBO was detected in 103 (85.8±3.2%) cases in patients with EB. It was significantly higher ($p<0.01$) in comparison with children of I group — 23 (46.0±7.0%) patients.

SIBO was determined in 37 (74.0±6.2%) patients with CGD (Hp-). In children of the control group the incidence of SIBO was significantly less ($p<0.001$) relative to patients with CGDP. The excessive microbial contamination of the proximal small intestine was diagnosed only in 4 (13.1±6.2%) children of the control group.

Analysis of the microbiological tests of faeces confirmed evidence that children with CGDP have violations of the normal ratio of the intestinal microbiota with the development of colon dysbiosis.

Thus, the normal composition of colon microflora was detected only in 2 (3.3±2.3%) children with DPUD and in 10 (8.3± 2.5%) patients with EB. It was significantly less ($p<0.05$) relative to children with CGD, where the normal ratio of the colon microflora was revealed in group II — in 10 (20.0±5.7%) cases and in group I — in 21 (42.0±7.0%) cases. The colon disbiosis was determined significantly more often in children with CGDP associated with Hp, in comparison with children of the control group ($p<0.05$), where the normal composition of the colon microflora was found in 23 (76.7 ± 7.7%) children.

The decreasing of the obligate microflora concentration was characteristic for patients with CGDP. Thus, deficiency of lacto-, bifidobacteria and E. coli was detected significantly more frequently ($p<0.01$) in children infected with Hp in comparison with children of the control group. The decrease in the concentration of lactobacilli was observed most frequently in patients with CGDP. It was detected in 52 (86.7±4.4%) children with DPUD, in 96 (80.0±3.7%) children with EB and in 32 (64.0±6.8%) children with CGD (Hp+). The growth of E. coli with mild enzymatic properties and hemolysing E. coli on the background of reducing the total number of E. coli was detected in children with CGDP. Reducing of obligate colon microflora in children with CGDP combined with the growth of conditionally pathogenic flora (Klebsiella, Proteus, Enterobacter, and others). The increased growth of conditionally pathogenic flora in children with erosive and ulcerative changes of the duodenum was identified in more than half of cases — 35 (58.3±6.4%) patients with DPUD, and 66 (55.0±4.5%) patients with EB. It was significantly more often in comparison with children with CGD ($p<0.01$). In addition, the increasing in the number of

Staphylococcus, Enterococcus and Candida was determined significantly more frequently ($p<0.05$) relative to patients of group I.

The analysis of systemic bacterial endotoxinemia level was conducted in patients with destructive changes in the duodenum mucosa. It was found that dysbiotic disorders of the intestinal microflora and long-term persistence of Hp is combined with a high concentration of LPS in serum, exceeding the normal values of this indicator. It was stated that the level of systemic endotoxinemia in patients with destructive changes in the duodenum mucosa significantly exceeded ($p<0.001$) indices of the control group (0.52±0.1 EU/ml). The highest LPS concentration in the blood serum was observed in patients with DPUD (2.1±0.1 EU/ml), and in patients with EB (1.9±0.1 EU/ml). Endotoxinemia, being within the physiological norm and not exceeding 1.0 EU/ml, was diagnosed in all children of the control group. Physiological level of endotoxinemia was detected only in 2 (10.0±6.7%) patients with DPUD and 5 (12.5±5.2%) patients with EB.

**Conclusions**

Therefore, CGDP associated with Hp occurs on the background of disorders in the quantitative and qualitative composition of the microbiota in the various parts of the digestive system. The most significant changes in the microflora ratio of the various biotopes of the intestinal develop in patients with erosive and ulcerative changes in the duodenum. It causes increased LPS absorption into the systemic blood flow and systemic endotoxin circulation. These changes should be considered in the treatment of these patients.

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Article presents the results of the diagnostics of the small intestine bacterial overgrowth syndrome, large intestine disbiosis and estimation of the systemic endotoxinemia in children with chronic gastroduodenal pathology. It is stated that progression of the chronic gastroduodenal pathology occurs on the background of persistence of Helicobacter pylori and combines with the abnormality of the ratio of intestine microflora of different intestine parts and development of large intestine disbiosis and small intestine bacterial overgrowth syndrome. Erosive and ulcerous diseases of the duodenum mucosa and microflora abnormality of different parts of digestive system in children cause the development of systemic bacterial endotoxinemia with the increased concentration of bacterial lipopolysaccharide in the blood serum above the physiological significance. It is necessary to take into account the detected microbiological changes to eradicate Helicobacter pylori during the treatment of the children with chronic gastroduodenal pathology.