**Kyoto consensus — a new etiological classification of chronic gastritis and its discussion**

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*Etiology is the causes and conditions of disease occurrence*
D.S. Sarkisov (1924-2000)

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Chronic gastritis — CG (gastritis chronica), as is known, it is the most common disease of the digestive system, accounting for 15-30% of the general population and 80-85% of all diseases of the stomach [15, 23, 26, 27]. V.H. Vasilenko explained by the fact that the stomach is the *"front edge"*, which assumes the *"first shot"* chemical, mechanical and thermal stresses of various kinds of food, which justifies its definition as *the "great sufferer"* [3].

While there is still no generally accepted international classification of most gastroenterological diseases [18], gastroenterologists all over the world are constantly developing, supplement and clarify the international classification of hCG. So, in 1990 at the IX International Congress of Gastroenterology in Sydney (Australia) adopted the *"Sydney classification system CG"* [22, 45]; in 1996 he published *"Houston option"* Sydney system, developed by a group of leading US gastroenterologists-Morphology [2, 19]; In 2002, the morphological classification of chronic atrophic gastritis has been developed [43, 44], and in 2008 — the classification system of atrophic gastritis *«OLGA» (Operative Link for Gastritis Assessment)* [40].

*New etiological classification HCG* was proposed in 2015 at the International Consensus in Kyoto (Kyoto, Japan), a group of international experts from Japan, the Netherlands, USA, Germany and Italy. According to the statement, the drafters of the authors, it aims to improve the diagnosis of chronic hepatitis as a disease that increases the risk of stomach cancer — gastric cancer [39].

The authors of the Kyoto consensus indicate that he does not cancel any *"Sydney classification system CG"* and her version of Houston, or *"OLGA" system,* but complements and refines their etiologic profile and recognize that the level of evidence — average.

**Classification of chronic hepatitis developed Kyoto consensus, proposes to distinguish the following forms of its etiology [39]:**

I. Autoimmune CG (etiology unknown, autoimmune pathogenesis)

II. Infectious CG:

1. *Helicobacter pylori* (Hp) induced HCG.
2. bacterial negelikobakterny CG:

a) caused by enterococci;
b) caused by mycobacteria;
c) caused by Treponema pallidum (lues).

3. Viral CG:

a) caused by an enterovirus;
b) caused by cytomegalovirus.

4. Fungal CG:

a) for the gastric mucormycosis;
b) for the gastric candidiasis;
c) at gastric histoplasmosis.

5. Parasitic CG:

a) caused by Cryptosporidium;
b) induced gastric strongyloidiasis;
c) induced gastric anizakiazom.

III. Exogenous CG.

1.Medicinal HH.
2.Alcoholic CG.
3.Radiation CG.
4.HCG caused Chemical substances.

IV.HCG caused Impact Specific reasons.

1.Lymphoblastic HCG.
2.Menetries disease (Menetrier P. E.) — giant Hypertrophic HCG.
3.Allergic CG.
4.Eosinophilic CG.

V. Secondary CG caused by other diseases:

1. HCG in sarcoidosis.
2. CG vasculitis.
3. CG in Crohn's disease (Cron gastritis).

In addition to the etiologic differentiation of HC, the Kyoto classification proposes to subdivide CG by morphological criteria: 1. by the severity (activity) of the inflammatory process and 2. by the degree of atrophic process and intestinal metaplasia in the gastric mucosa (LL), which increase the risk of developing gastric cancer (RJ). Morphological data obtained by sighting endoscopic gastric biopsies of the antrum and corpus and setting inflammatory process activity and severity coolant atrophy, atrophic morphological classification according hCG [40, 44].

Special studies on a large clinical material (98 thousand patients) found that in atrophic forms CG RZ develops in 0.8% of patients, with intestinal metaplasia — in 1.8%; with mild to moderate epithelial dysplasia — 3.9 at%, and in severe (expressed) dysplasia — at 32.7% [36].

To determine the severity of atrophic process in the coolant and the risk of gastric cancer is also recommended to use a serological test, — determination of pepsinogen and pepsinogen-I-II: the lower the level of pepsinogen-I and -II, the higher the coolant atrophic process and the risk of gastric cancer [39].

Compilers Kyoto consensus is recommended for the prevention of gastric cancer to follow a policy of eradication of *Helicobacter pylori* (Hp), indicating that its effectiveness depends on the severity, stage and grade of atrophy of the coolant before the course of eradication therapy (minor when lost at least 30% of the gastric glands, moderate — 30-60% and heavy — more than 60%). In severe atrophy of the coolant occurs *"point of no return" when* the Hp eradication was able to prevent the development of gastric cancer. To increase the effectiveness of Hp eradication, the authors of the Kyoto consensus suggest determining the individual sensitivity of the isolated strains of Hp to antibacterial drugs used for their eradication.Considering the increasing resistance of Hp to eradication therapy from year to year, they consider it expedient to develop optimal schemes for Hp eradication for different regions of the world.

The consensus for the first time, the authors recommend to take into account the fact that in various forms of infectious CG noted Hp interaction with other microflora, colonizing coolant [39].

**Discussion. I.** Some authors, analyzing the content of Kyoto consensus claim that the new etiologic classification of CG *for the first time suggests that its etiology, in addition Hp, can be set to other micro-organisms (bacteria, viruses, pathogenic fungi and parasites).* But this statement is erroneous. In *"Sydney classification system"* in the *"Special forms of hCG"* was isolated *"Infection variant hCG (besides* Hp)», wherein the etiologic agent Include: *Helicobacter heilmanni, Treponema pallidum,* cytomegalovirus, and fungi of the genus*Candida* [22, 45]. In the *embodiment of Houston* "Sydney System" in the *"etiological factors of CG"* is also available See *"Infection hCG (other than Hp)»,* where the etiological hCG factors mentioned bacteria, viruses, parasites and pathogenic fungi (without specifying the type of agent) [2, 19].

**II.** The *"Kyoto consensus" as* a major cause of chronic hepatitis called **Helicobacter pylori (Hp)-infection.** And this is no surprise to us, because it is part of its authors-compilers we found

P. Malfertheiner names (Germany) and DY Graham (USA) — the most orthodox adherents the concept of the leading role of Hp in gastroduodenal pathology [39].

Indeed, Hp-infection is widespread in the world: Hp colonizes the gastric mucosa (GM) in 60% of NACE Lenia globe on every continent, but the clinical implications of their life are determined only 1% of them [8]. Approximately 70% of people infected with Hp, — it is healthy bacillicarriers often — throughout their lives [1].

Hp is a non-invasive microorganism whose vital activity is limited to the gastric compartment — it can not exist even on the mucous membranes of neighboring organs — in the duodenum and in the esophagus, with the exception of the foci of gastric metaplasia. In the stomach, Hp is found only in the epinepthelial mucus, on the outer surface of a single-layered cylindrical epithelium of the stomach (between villi) and in the intercellular space. Neither in the subepithelial layer, nor in the epithelium of the gastric glands Hp, as a rule, is not detected.

One of the discoverers of the bacteria Hp (B. J. Marshall), in order to prove its etiological role in chronic hepatitis and peptic ulcer disease, has made an experiment with self-infection Hp: he introduced himself in the stomach concentrated suspension of pure culture of Hp $^{(10}$ September microbial bodies). 7 days later, he developed the typical clinical picture of acute gastritis, which promptly stopped **without any consequences** [8].

*Renowned microbiologist SV Sidorenko believes that "widespread Hp-infection in persons with no signs of disease — is a strong argument that refutes the leading role of Hp in gastroduodenal diseases" [12]. And outstanding domestic pathologist IV Davydovskiy stated: "The causal link — a necessary connection. Hence the continuity of cause and effect, their unity... The reason that does not work, do not have a reason,* "[4*]*.

In connection with the above, we decided to study *the microbial "landscape"* of the stomach and properties of bacteria vdelennyh modern methods of microbiological examination. In order not to Emerged doubts about the reliability of our results, *we have decided to give us a detailed description of the used microbiological methods.*

**Techniques.** We examined 37 patients with antral atrophic HC, 25 patients. — with erosive CG, 9 people. — with atrophic CG (focal and diffuse), — a total of 71 patients with various forms of CG. The mean age of patients was 54.9 ± 4.93 years; 60.7% of men, 39.3% of women. Control group — 62 people.

Biological samples were obtained from the antral and base sections of the coolant for gastrofibroscopy by targeted biopsy using sterile gastrofibroscope pliers. Pre-treated the mouth with an antiseptic. Five samples of the biopsy specimen were prepared, which were placed in 0.3-0.5 ml of buffered saline and immediately (within 15 minutes) delivered to the laboratory to preserve the anaerobic microflora. Some of the fragments of the obtained gastric tissue after extraction of the gastrofibroscope forceps were removed with a dissecting needle and, without washing with water, were placed in a 10% formalin solution for 24 hours for light microscopy.

Next: two pieces of biopsy material were dehydrated, degreased and paraffin filled in a histological device according to the generally accepted method. From the paraffin blocks, slices 5 μm thick were made on 10-12 slides. Histological and cytological preparations were stained with standard solutions Dyes.

To carry out bacteriological studies, one of the remaining three pieces of the biopsy carefully Homogenized on vortex (Lachema), Then sowing of biological material on a petri dish with nutritious helicobacterial blood agar with special biological additives Biomerieux and subsequent incubation in anaerobic Gas generator packages AnaeroHiGas — Campylo Pack (Himedia) or Microaeropbil (Becton Dicinson). Another piece of the biopsy with the aim of The enrichment was placed in a thioglycolic medium (control medium Sterility — SCS). The last piece was used for urease test (using test strips or Biomerieux test microplate Lachema) previously conducted bacteriological seeding method smears on nutrient media, defined above,followed by incubation in Anaerobic.

The study of the microflora of the stomach included its quantitative (from dense media of primary culture) and qualitative analysis (from enrichment media). Studied representatives of aerobic, anaerobic and facultative anaerobic microflora and fungi of the genus *Candida.*

Microscopy of drugs stained by Gram was carried out after obtaining visible growth of microorganisms in broth culture of SCS nutrient medium (usually within two days of incubation in the standard mode). In the absence of a visual growth of bacteria colonies in SCS, the thermostating was prolonged to 15 days. In other cases, after 5-7 days of incubation of biological samples on Petri dishes, the microflora growth pattern was evaluated. The differential diagnosis of microorganisms was carried out according to our schemes [6, 7] and regulated by regulations and rapid diagnosis tests using commercial systems corresponding profile of the microorganism. Hp identification was carried out by classical and improved (modified) our method protected by the patent of the Russian Federation (2006) [1].

The total antibodies of classes IgA, IgM, IgG to the CagA (Hp) antigen were determined by ELISA using the Helicobacter-antibody test system (ZAO Vector-Best, Russia) using the StatFax-ZOZ and Multiskan devices. When evaluating the results of the study, a determination of antibody titer was used, with titres 1:10 and higher (1:20, 1:40, 1:80) being considered diagnostic, treating them as positive and sharply positive.

To confirm the biological compatibility of the strains of the isolated bacterial microflora of coolant as additional methods, their phenotypic (tinctorial, cultural, biochemical) characteristics, as well as phage susceptibility and sensitivity to antimicrobials, were compared.

In accordance with the recommendations of the "Maastricht Konsa Sousa-4" (2010), was used for determining Hp noninvasive scatological immunochromatographic test antigen with monoclonal anti-Hp antibodies (ImmunoCard STAT HpSA Germany), wherein before the study sample was pre-diluted in 2-fold. Then 3 drops of the resulting solution was introduced into a test system, and *as it moves the sample fixed during the appearance of violet staining control band.* Interpretation of the results was carried out not earlier than 10-15 minutes.

Factors of virulence of enterobacteria and non-fermenting gram-negative bacteria were attributed to adhesive activity, which was taken into account in cell cultures of HEp-2 and HeLa, in human erythrocyte tests or in the formation of a wall ring on meat-peptone broth. Capsule formation was studied using coloration according to the Burry-Hins method, and an increased level of mucus formation — visually on the plates of native growth of microbial culture.

The lack of mobility in mobile bacteria was found to be 0.4% by semiliquid agar, and the absence of lactose decomposition in lactose-positive species — on Olkenitsky agar and Endo medium. Thiol-dependent hemolysin was detected by culture of bacteria on the nutrient medium for its production; α-hemolytic activity — by injection daily agar culture mikroorga nism 2% Hottinger agar with 5% suspension of erythrocytes rabbit; DNA-aznuyu activity and proteolytic enzymes — in a medium with milk and litmus; With milk and methylene blue; With gelatin, and Breathing intensity — with Congo red dye Methodologies AV Aleushkinoy [1].

When studying staphylococci, the products Plasmacoagulases, lecithovitellases, DNA-ase, as well as their Persistent properties — antilizimic, anti-interferon activity.Anticomplementary activity was assayed by the method of O. V. Buharina [13].

The ability of corynebacteria to produce Hemolysins were determined on 5% blood agar.

Virulence of streptococci was studied by determining their hemolytic activity on 5% blood agar with erythrocytes of ram, and their ability to decompose sodium hippurate was also investigated.

An important indicator of virulent bacteria is their ability to decompose urea (urease activity). Regardless of the recommended standard methods, all strains isolated by us were tested for this feature. It is known that, thanks to this very property of Hp, it is possible to significantly reduce the acidity of the gastric juice and thereby increase their adaptive abilities.Combinations of test strips with urea ("VioMegieuh"), the liquid nutrient medium with urease were used, the test microplate («Lachema»).

The antibiotic susceptibility of isolated strains of microorganisms was also studied by the disk-diffusion method in terms of the diameter of the growth retardation zone in the Biomeraeux nutrient medium. The turbidity of the bacterial suspension added to the agar surface corresponded to 0.5 Ed by the McFarland scale and was determined using a Densi-La-meter-II apparatus (Lachema). The paper discs were used with antibiotics and production Himedia NITSF — no less than 12 of the drug core groups [10]. The results of the study were evaluated by comparing the diameter of the zones of the tested microorganism with the diameter of the growth inhibition zones and the minimum inhibitory concentration (MIC) of a specific antibacterial preparation.

When studying the sensitivity of anaerobic bacteria to antibiotics, the serial dilution method in a liquid nutrient medium was used. Determination of β-lactamase production in enterobacteria and nonfermenting Gram-negative bacteria was carried out by *"double disc"* E-test and Oxoid test, and the determination of β-lactamases production of Gram-positive bacteria used nitrotsefinovye wheels and iodometric method on paper strips.

Resistance to oxacillin in staphylococci was studied by screening method (on a plate with 4% salt agar containing 6 μg / ml oxacillin), as well as by disco-diffusion method with latex agglutination to reveal the penicillin-binding protein (PSB).

The study used reference strains of bacteria from the collection of GISK them. JI.A. Tarasevich.

Digital analysis of the data was performed Pomo schyu Biostat statistical package for Windows, version 4.03 and Excel spreadsheets.

**The results of research.** Microbiological screening in the surveyed patients with CH revealed the presence of 80.3% of them in the presence of coolant 105 different species of bacteria, including 55.7% of cases — in the form of microbial associations. Most often, when hCG met: *of Streptococcus spp.* — in 52.5% of cases in a concentration of 4,4 Lg cfu / g;*Staphylococcus spp.* — 23% at a concentration of 2,1 Lg cfu / g and fungi of the genus *Candida* (19.7%) — 1.7 Lg cfu / g. The presence of Hp was found in 18% of patients with hCG at a concentration of 3,6 Lg cfu / g and usually in association with other bacteria. In addition, they were allocated *Peptostreptococcus spp.* (11.5%), *Enterobacteriaceae sp.* and*Corynebacterium spp.* (no 9,8%) and other (less than 6.5%), — in total — 24.9% [21].

The highest degree of colonization set in *of Haemophilus spp.* (5 Lg cfu / g), and *Streptococcus spp.* (4,4 Lg cfu / g) and average concentration of microbial cells in biopsies coolant amounted 3,4 Lg cfu / g.

When studying virulence properties derived from bacterial microflora in coolant hCG *urease activity* was determined at 27,3 ± 6,0%; natural or acquired in the process of adaptation to the aggressive environment of the stomach pathogenicity factors — from 36,3 ± 6,5%, and resistance to various antibiotics — in 45,5 ± 6,7%, including production of β-lactamase and antibacterial resistance to the leading Drugs, used in schemes eradication Hp (klaritromitsmn, ampicillin, metronidazole, tetracycline).

In general, the signs of pathogenicity set at 56.4 ± 6.7% of the coolant at vdelennyh hCG bacterial strains, including interferon and antilysozyme activity. All microorganisms were isolated part mucosal microflora (M-microflora) stomach had adhesiveness, and most of them — invasiveness (unlike Hp) and pathogenic properties. This allows us to consider them as potential etiological factors for the development of infectious-inflammatory processes in the coolant when hCG, together with Hp, and possibly without them [16, 21, 23, 25, 30].

By the way, enterococci, which are featured in the *"Kyoto consensus"*, as one of the etiological factors of bacterial hCG, were identified by us only in 9.8% of cases, and mycobacteria — even rarer.

*It should be noted that the effectiveness of eradication therapy with hCG, associated with Hp, can't serve as proof of the exceptional etiological role of Hp in its development, sinceat the same time destroyed the whole bacterial microflora of the stomach, not only Hp.*

**III. HCG and gastric cancer (GC).** *"Kyoto consensus"* attaches primary importance in the development of gastric cancer Hp-infection and atrophic process and intestinal metaplasia in the coolant, and International Agency for Research on Cancer (International Agency for Research on Cancer — IARC) Hp UN recognized class I carcinogen. Is it justified? It is known that gastric cancer develops in only 1% of those infected Hp. In addition, Hp is not a causative factor RG (etiology unknown), does not produce carcinogenic and mutagenic substances and carcinogenic role assumption Hp mainly based on epidemiological data.

In Africa, in India, where the population of Hp infection reaches 90-95% GC is much rarer than in Europe and the USA, where Hp colonization of the coolant does not exceed 35-50% [31, 32, 41]. According to R. Correa (USA) — a leading expert on the issue of RJ — RJ Development — a multi-stage and multi-factor process extended in time. First, developing non-atrophic antral CG, then for 20-25 years or more there is a slow progression of atrophic process in the coolant (with soon Stu 0,6-3,3% per year), after which the coolant comes intestinal meta Plaza, and after it — epithelial dysplasia (precancer), and finally AJ [32].

Recently, at a working meeting of the European Group for the study of the NIJ Hp-infection — EHSG (Ljubljana, 2012), this concept of *"cascade"* has been shaken. Thus, the report V. Varbenova et al. It was represented Lena evidence that the development of gastric cancer does not correlate with the severity of atrophy and intestinal metaplasia in the coolant by OLGA system, and in studies M. Leia et al. it was found that in most cases GC proceeds with normal pepsinognena- I and pepsinogen-II, indicating the absence of atrophy in the emulsion [28]. Thus, atrophic process in the coolant and intestinal metaplasia are not, apparently, a mandatory step in the development of gastric cancer.

Increased risk of gastric cancer and marked with *autoimmune* fundal atrophic hCG not bound to Hp-infection, which 40% of the proceeds in conjunction with megaloblastic *("pernicious")* anemia Addison-Biermer [23, 24].

*In the last revision of the "Maastricht Consensus" (MK-4, 2010) it was made an important recognition: "After the eradication of Hp improved functionality of the stomach body, but how it is related to regression of atrophy remains controversial. Convincing evidence that Eradication Hp leads to regression of intestinal metaplasia, has not been obtained " [20, 34].*

It is important to emphasize that the value of the data Hp-infection in gastric cancer development include only the distal (piloantralnomu) RJ and proximal (cardia) gastric cancer is not associated with Hp. Moreover, there is credible evidence that the presence of Hp in antrum of the stomach, especially their of CagA-positive strains, somehow prevents the development of gastric cancer and cardia adenocarcinoma of the distal esophagus, performing a protective role [35, 37].

*In connection with the foregoing, F. Roccas concluded that " the relationship between Helicobacter pylori infection and the subsequent development of gastric cancer is unclear epidemiological paradox" [11].*

*The "Kyoto consensus" states: "Eradication of Hp pos Wola achieve maximum effect for the prevention of gastric cancer in its conduct prior to the development of atrophic CG" [39]. At the same time, an authoritative scholar problems AJ* P. Correa *asks the question: "Is RJ prevention possible?» (Is gastric cancer is preventable?) [33]. A J. Personnet sarcastically noted that "attempts to prevent the development of gastric cancer by eradication of Hp (antibiotic therapy — J. Ts) are trying to prove that in the era of the deciphered the human genome can be cured with the help of AJ antibiotic therapy" [42]. Furthermore, since the Hp infected several billion of the world population, an effective eradication therapy to prevent unrealistic GC [33].*

**IV. Alcoholic hCG.** The claim that spirits can cause chronic hepatitis *("Kyoto consensus 2015"),* are not supported by most modern gastroenterology. It was found that the systemic administration of concentrated alcohol solution can be a *causative factor of acute alcoholic gastritis* (OAS) due to violation of local blood flow (microcirculation in the coolant), destructive and degenerative processes (desquamation of epithelium, and necrosis), the

development of inflammatory neutrophil infiltration coolant. However, studies have shown that these lesions are generally reversible and often end in a complete restoration of the structure and functions of the coolant without transformation in alcoholic hCG [9, 15, 23, 26, 46].

The International Classification of Diseases and Related Health, 10 revision (ICD-10, 1995), there is a heading *"Alcoholic gastritis"* (K.29.2 code), but without specifying the acute or chronic alcoholic gastritis.

**V. Chemical hCG,** in our opinion, should include: 1. *a drug HCG* (NSAIDs, corticosteroids, tetracycline, sulfonamides, and others.); 2. *professional hCG,* due to prolonged exposure to toxic chemicals (vapors fatty acids and alkalis; charcoal, silicate, cotton, steel dust, radiation, chemical synthetic products, benzene, chromium, etc.). 3. The *effect of detergents* (toxic bile acids, lysolecithin), systematically are thrown into the stomach from the duodenum during duodenogastric reflux — GDR (reflux gastritis) [4, 7, 45].

Compilers *"Kyoto consensus"* have to admit that many of the aspects debated [39], and it is difficult not to agree.

In the last 15-20 years in gastroenterology has spread *"fashion"* on the consensuses (conciliation meeting): *"The Maastricht Consensus", "Rome Consensus", "Kyoto consensus",* etc., which is contrary to the basic principles of EBM (evidence-based medicine). requiring no agreement, and evidence-based clinical reasoning, analysis and synthesis of scientific and clinical evidence [14]. Conciliation meeting lead to the fact that the doctor becomes a simple technical executive of the developed recommendations that, based on the fundamental principles of medical practice is unacceptable.

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**Kyoto consensus — a new etiological classification of chronic gastritis and its discussion**

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**Key words:** chronic gastritis, etiology, Helicobacter pylori, gastric cancer, Kyoto consensus

The article provides a detailed analysis of the provisions of the Kyoto consensus on the classification of chronic gastritis. Particular attention is paid to the etiological role of Helicobacter pylori. The authors presented the results of their own study of the microbial "landscape" of the gastric mucosa. The role of Helicobacter pylori, atrophy and metaplasia of the gastric mucosa in the development of gastric cancer, as well as other etiological variants of chronic gastritis: alcoholic, medicinal, etc. are discussed. Critical assessment of the main provisions of the Kyoto consensus was made.