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CHRONIC PHARYNGITIS: ETIOLOGY, PATHOGENESIS, TREATMENT. NEW APPROACHES TO THE ESTIMATION OF ETIOPATOGENESIS

Abstract

The paper discusses modern approaches to etiopathogenesis assessment and treatment of chronic pharyngitis. The results of mass spectrometry of microbial markers (MSMM), a modern method for the diagnosis, use are presented. The method allows to detect the microorganisms in a biofilm, in a "sleeping state" under the protection of mucin. With the help of this STAT-method, it is possible to detect 57 biomarkers of microorganisms in the smear from the pharynx at the same time, 2 hours after delivery of the sample to the laboratory. It was found that 91% of the examined patients with chronic pharyngitis (n = 62) show increased total content of microorganisms, which indicates the need for antibacterial therapy; 87% of patients have elevated levels of endotoxin, which is a sign of general intoxication; 71% of patients have reduced plasmalogen level and these patients may be at increased risk for lipid metabolic disorders; in 100% of the examined patients with frequent exacerbations of chronic pharyngitis the nasopharyngeal microflora (Cocci) in the pharynx is determined, as well as new etiopathogenetically significant microorganisms (not detected by PCR and cultures), among which there are 7 transient microorganisms (normally their level in the pharynx is zero), 11 resident microorganisms (6 — found in the pharynx in normal condition on the minimum level, and 5 with high levels in normal condition). Also, with the help of MSMM, a significant or moderate increase in herpes simplex virus and cytomegalovirus was detected in the majority (75%) of patients, which indicates the important role of the viruses of this group in the etiopathogenesis of recurrent chronic pharyngitis; level of Candida spp. is increased in half of patients; and normal

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microflora is increased in 71% of patients, which indicates the preservation of local resistance in patients with chronic pharyngitis, who were examined by the authors. Thus, the use of MSMM in chronic pharyngitis allows to identify new etiopathogenetic microorganisms and prescribe more effective treatment on this basis. Thus, it is possible to carry out personified, more effective treatment.

Key words: *chronic pharyngitis, mass spectrometry, immunity, dysbiosis, pathogenesis, laboratory diagnostics, antibacterial agents*

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HIV — human immunodeficiency virus, GERD — gastroesophageal reflux disease, GIT — gastrointestinal tract, MSMM — mass spectrometry of microbial markers, AP — acute pharyngitis, P — plasmalogen, PAS — peroxidase activity of saliva, BOS — bacterial overgrowth syndrome, IBS — irritable bowel syndrome, CVS — cardiovascular system, CP — chronic pharyngitis, EBVI — Epstein-Barr viral infection

Introduction

Chronic pharyngitis (CP) is a widespread disease of the upper respiratory tract characterized by inflammation of the pharyngeal mucosa. Up to 7% of adults in Russia and Western countries [3, 4] suffer from CP. In outpatient practice of otolaryngologists, CP occupies a leading place (up to 70% of visits) [19]. Patients with CP can also be treated by general practitioners, therapists, immunologists, so the number of patients with CP is higher than indicated in the statistics.

CP is characterized by pain, tickling, discomfort in the throat, sleep disturbance, complaints of constant runoff of mucus along the back wall of the pharynx ("lump" of mucus, coughing). These symptoms significantly worsen the quality of life of patients. In case of recurrent CP, different parts of the pharynx can be affected: nasopharynx, oropharynx, larynx, often the inflammatory process is descending in nature. Morphological changes of the mucous membrane in CP are predominantly localized in one of the anatomical parts of the pharynx, which allows to allocate individual nosology, for example, chronic nasopharyngitis [42].

Professional hazards, long-term load on the vocal apparatus (singers, teachers), climatic conditions, pathology of internal organs contribute to the recurrent course of CP. It should be borne in mind that the pharynx and gastrointestinal tract (GIT) represent a single system: nasopharynx is the initial part of the gastrointestinal tract. Acid content in GERD (gastro-esophageal reflux disease) may fall from the stomach into the pharynx (normally, pH in the oral cavity is alkaline), including during sleep [41]. Other diseases of GIT contribute to recurrent CP: gastritis, bacterial overgrowth syndrome (BOS), irritable bowel syndrome (IBS). Diseases of the cardiovascular system (CVS), female genital area, cervical osteochondrosis, apnea contribute to the chronic course of the inflammatory process in the nasopharynx [7]. Recurrent CP is usually difficult to treat. Repeated therapy by otorhinolaryngologists, immunologists leads to a temporary remission of the disease. In connection with the above, the study of etiopathogenesis, the development of new approaches to the diagnosis and treatment of CP are relevant.

Etiology and classification of chronic pharyngitis

Chronic pharyngitis is often caused by infectious agents: viral, bacterial, fungal, CP of mixed etiology, and it also can have allergic or traumatic (due to foreign body contact or surgery) nature. CP can occur due to irritating factors (hot liquid or steam, acids, alkalis, radiation, etc.), diseases of the gastrointestinal tract, CVS, etc.

Chronic pharyngitis usually is classified according to the nature of the developed mucous changes: catarrhal (simple), atrophic or subatrophic and hypertrophic (hyperplastic, granulosa). These forms of chronic inflammation are often combined. Thus, the presence of diffuse atrophic changes in the mucous membrane can be combined with focal hyperplasia of the lymphoid tissue of the posterior pharyngeal wall or tubopharyngeal ridges (hyperplastic process develops).

Viral infection in ARVI is often the first phase of CP, it "paves the way" for subsequent bacterial infection [24]. A common form of acute inflammation of the pharyngeal mucosa is catarrhal pharyngitis in ARVI. About 70% of acute pharyngitis (AP) is caused by viruses, among which rhinoviruses, coronaviruses, respiratory syncytial virus, adenovirus, influenza and parainfluenza viruses are more common. The most typical pathogens of AP are rhinoviruses [34]. In descending order of frequency, viruses with acute pharyngitis [45] can be listed as follows:

- rhinoviruses
- coronaviruses
- adenoviruses
- influenza virus
- parainfluenza virus

Rare viruses:

- respiratory syncytial virus
- herpes simplex viruses (types 1 and 2)
- enteroviruses
- Coxsackie virus
- Epstein-Barr virus
- cytomegalovirus
- human immunodeficiency virus (HIV), the clinical significance of HIV in the development of CP has increased significantly in recent years [39].

Currently, it is shown that rhinoviruses are responsible for more than 80% of ARVI cases during the autumn epidemics.

Among bacterial pathogens in AP, the leading role belongs to group A β-hemolytic Streptococcus: 15–30% of cases in children and 5–17% of cases in adults. Relatively rarely (less than 5%), AP or exacerbations of CP can be caused by group C and G streptococci [32]. In 90% of cases bacterial flora of the posterior pharyngeal wall is represented by associations of 2–3 types of microorganisms [33].

Pharyngitis can be **classified** as follows.

By severity of the symptoms:

- acute
- chronic

By etiological factor:

- viral
- bacterial
- fungal
- allergic
- traumatic, including post-tonsillectomy
- caused by irritant factors, including smoking
- caused by GIT diseases (GERD, hiatal hernia, chronic gastritis, including atrophic, BOS, IBS, functional GIT disorders, chronic cholecystitis, pancreatitis).

There are types of pharyngitis associated with specific pathogens:

- Epstein-Barr virus in infectious mononucleosis
- *Yersinia enterocolitica* in Yersinia pharyngitis
- gonococcus in gonorrheal pharyngitis
- *Leptotrixbuccalis* in pharyngeal leptotrichosis.

By the nature of inflammation:

- hypertrophic (granulosa)
- atrophic (points to involutional changes in the pharynx, pathology of internal organs and systems (gastrointestinal tract, reduced metabolism))
- catarrhal
- mixed form.

Clinical picture of chronic pharyngitis and main mechanisms of its pathogenesis

The clinical picture of chronic pharyngitis is characterized by tickling, dryness, discomfort and pain in the throat when swallowing. Patients complain of a "lump of mucus" in the throat, which causes a desire to cough. In the case of inflammation of tubopharyngeal ridges, pain usually radiates to the ears. Palpation may cause pain and enlargement of upper, anterior and/or posterior lymph nodes. During pharyngoscopy, hyperemia of pharyngeal posterior wall and palatal arches, separate inflamed lymphoid granules are seen, while hyperplasia of the tonsils can be noted. Sings of tonsillar inflammation, which are typical of tonsillitis, are often absent. Exacerbation of chronic pharyngitis or acute pharyngitis may be the first manifestations of some infectious diseases: measles, scarlet fever, rubella. In some cases, differential diagnosis with Kawasaki disease and Stevens-Johnson syndrome is required [23].

The clinical picture of chronic pharyngitis is not characterized by fever, deterioration of the general condition (weakness, chills). Patients experience frequent ARVI, nasal congestion, prolonged, dry, sometimes paroxysmal cough. This violates the quality of life: discomfort in the throat is associated with the need to constantly swallow the mucus located on the back wall of the pharynx, breathing

becomes heavier in sleep, this makes patients irritable, forces them visit a doctor.

The course of the chronic inflammatory process on the posterior pharyngeal wall depends on the nature of the microflora, its virulence, the degree of contamination, the state of the macroorganism, local immunity, the mucous membrane itself: its innervation, circulation, degree of hydration [28]. The mucous membrane of the pharynx has a complex composition: muscular, nervous, vascular, secretory and lymphoid parts. The pharynx is an important regulator of reflex stimuli, inhibition of the respiratory act, delay in swallowing. With the help of the pharynx, the following functions are carried out: voice formation, speech, respiratory act, moving food along the esophagus.

Pain in acute pharyngitis and exacerbation of CP is due to the rich innervation of the pharynx [3]. The pharynx receives sensitive, motor and vegetative innervation from the pharyngeal plexus located on the outer surface of the middle sphincter of the pharynx under the buccopharyngeal fascia. This plexus is formed by the branches of the pharyngeal and vagus nerves, as well as sympathetic fibers of the upper cervical ganglia. Sensitive innervation of the pharynx is mainly carried out by the pharyngeal nerve, but in the pharyngeal ostium of the auditory tubes there are nerve connections with the second branch of the trigeminal nerve. The superior laryngeal nerve ("branch of vagus nerve") is also involved in the innervation of the hypopharynx. Rich nerve connections explain the possibility of pain irradiation in diseases of the pharynx to the ear, lower jaw [16].

With atrophic pharyngitis, the mucous membrane of the pharynx looks thin, dry, often covered with dried mucus. Injected vessels can be seen on the shiny surface of the mucous membrane. Smoking and tonsillectomy often lead to the development of atrophic changes in the mucous membrane of the pharynx [24].

In hypertrophic form, pharyngoscopy reveals pockets of hyperplastic lymphoid tissue scattered on the back of the throat, or enlarged tubopharyngeal ridges located behind the rear palatine arches.

During exacerbation of CP, these changes are accompanied by hyperemia and edema of the mucous membrane. In CP, objective changes may be less pronounced than symptoms experienced by patients.

Constantly difficult nasal breathing contributes to the development of chronic pharyngitis. CP may be caused not only by the transition to breathing through the mouth, but also by abusing vasoconstrictor nasal drops, which flow down from the nasal cavity into the throat and have excessive anematizing effect [39]. Symptoms of pharyngitis may be present in postnasal drip. In this case, discomfort in the throat is associated with the flow of pathological secretion from the nasal cavity or paranasal sinuses along the back wall of the pharynx. In addition to constant coughing, this condition can cause, more often in children, the appearance of wheezing, which requires differential diagnosis with bronchial asthma.

The following factors contribute to the development of chronic pharyngitis:

- constitutional features of pharyngeal and GIT mucous membrane structure;
- long-term exposure to exogenous factors (dust, hot dry or smoky air, chemicals);
- difficulty in nasal breathing (breathing through the mouth, decongestants abuse);
- smoking and alcohol abuse;
- allergic diseases (pollinosis, food allergy);
- endocrine disorders (menopause, hypothyroidism, metabolic syndrome);
- vitamin deficiency (Vit A);
- diabetes;
- heart, lung failure;
- renal failure;
- violated intestinal microenvironment system (BOS, IBS, etc.).

Disorders in the pharyngeal and intestinal microenvironment (dysbiosis) play a significant role in the development and maintenance of chronic inflammatory processes of the posterior pharyngeal wall [20, 22].

The formation of dysbiosis in different parts of the digestive tract is possible in the case of disruption of the physiological balance between the factors of resistance and aggression. The following contribute to the development of microenvironmental disorders: non-compliance with sanitary and hygienic standards, the use of certain drugs (antibiotics, etc.), the presence of severe chronic, allergic diseases, immunodeficiency conditions.

Chronic pharyngitis may be associated with GIT pathologies: chronic gastritis (atrophic), gastro-

esophageal reflux disease (GERD), cholecystitis, pancreatitis. Entry of acid gastric contents into the pharynx during sleep in GERD and hiatal hernias is often a hidden cause of chronic catarrhal pharyngitis. In this case, treatment is ineffective without eliminating the main cause of the disease [27].

The quantitative and qualitative composition of normal microflora (in oral cavity, upper respiratory tract, intestines) in a healthy person is quite stable. The microenvironmental phenotype of the person is influenced by genotypic characteristics and environmental factors. In case of CP, violations of pharyngeal microenvironmental mucosa were revealed. Under normal conditions, microorganisms living on the mucous membrane of the oropharynx cannot penetrate into the deep layers of tissue and develop an infectious and inflammatory process. Invasion due to the synthesis of enzymes is possible with the development of dysbiosis of the mucous membrane of the pharynx, associated with the inhibition of specific and nonspecific factors of the macroorganism natural reactivity. This is manifested by a local violation of the mucociliary barrier, blood circulation, increased permeability of the vascular wall, and at the first stage of inflammation — by an increase, and subsequently — a decrease in the level of neutrophils, lymphocytes, phagocytic cells, the development of local and general immunosuppression, activation of transient and opportunistic pathogenic resident microflora, with the development of chronic inflammation in the tissues of the posterior pharyngeal wall, tonsils [8]. In chronic inflammation in the mucous membrane of the nasal cavity, paranasal sinuses, larynx and trachea, focal or diffuse metaplasia of the multirowed columnar epithelium occurs with formation of multilayer epithelium without cilia. Such a modified epithelium loses the ability to remove bacteria and viruses from its surface by active mucociliary transport.

With a persistent, unmanageable course of CP and the presence of complaints, differential diagnosis is carried out with a number of syndromes that develop in some systemic diseases and diseases of the nervous system. Plummer-Vinson syndrome occurs in women aged 40 to 70 years secondary to iron deficiency anemia. Sjogren's syndrome is an autoimmune disease accompanied, in addition to the pronounced dryness of the mucous membrane in gastrointestinal tract, by a diffuse enlargement of salivary glands. Eagle syndrome (stylalgia) is characterized by strong, constant, often unilateral pain in the throat caused by a longer styloid process, which is located on the lower surface of the temporal bone and can be felt over the upper pole of palatine tonsil. A number of neuralgia (glossopharyngeal or vagus nerve) can also cause pain in the throat, especially in the elderly.

Thus, chronic pharyngitis is often not an independent disease, but a consequence of the pathological condition in other organs and systems, and this makes the task of its treatment very difficult sometimes.

Diagnosis of chronic pharyngitis

Diagnosis of CP is carried out using a set of modern methods:

1. Survey — detection of complaints, clinical symptoms (sore throat, tickling, runoff of mucus on the back of the pharynx, additional symptoms — dry mouth, dry, paroxysmal cough).
2. Physical examination: inspection of the posterior pharyngeal wall (by pharyngoscopy), palpation, ultrasound examination of neck lymph nodes (submandibular, anterior and posterior cervical), most often on pharyngeal posterior wall hyperemia, edema, atrophy of the mucosa, formation of different sizes of the granulomas (hyperplasia of mucosa) are revealed in CP.
3. Laboratory test. The standard for laboratory diagnosis in CP is a culture of a smear taken from the posterior pharyngeal wall to determine the etiologically significant microflora (bacterial, fungal), and diagnosis is carried out using PCR: diagnosis of chlamydial, mycoplasma, viral microflora (herpes viruses — 1, 2, 6 types, cytomegalovirus, Epstein-Barr virus) [35].

An innovative method for diagnosis of chronic pharyngitis

With constant complaints from patients with CP, etiologically significant microorganisms often cannot be determined. In this regard, the introduction of new diagnostic methods for CP is

extremely important. More than 20 years ago, the method of mass spectrometry of microbial markers (MSMM) was developed and recommended for diagnostic use, allowing to detect 57 markers of microorganisms in the smear from the pharynx (by the level of fatty acids, aldehydes, for comparison — 12–15 microorganisms are detected using culture). When carrying out MSMM, the content of genetically stable biomarkers of microorganisms — anaerobic cocci, actinomycetes, gram-negative microorganisms, enterobacteria (HP, Campylobacter), fungal, viral markers is determined. The result and the conclusion are given, in which quantity of each microorganism in 1 ml of a biological sample is shown. The result can be issued 2 hours after the transfer of the biomaterial to the laboratory [36]. The introduction of this method into practice is currently difficult due to certain challenges in the interpretation of the results (60 indicators). Our work presents the experience of using MSMM in chronic pharyngitis.

Treatment of chronic pharyngitis. General principles of treatment

In the initial stages of the disease, treatment is carried out by otolaryngologists, and after repeated courses of therapy with insufficient clinical effect, patients seek help from immunologists.

Otorhinolaryngologists usually carry out complex treatment — sanitation of the nasopharynx with local antiseptics, anesthetics are used for pain, and washing of tonsils is carried out (with the combination of CP with exacerbation of chronic tonsillitis). After the detection of pathogenic microflora, in the presence of signs of intoxication, fever, inefficiency of local antiseptics, antibacterial therapy is prescribed, taking into account sensitivity — it can be antibiotics of the penicillin class or other groups, macrolides, and when detecting viral or fungal agents, antiviral and antifungal drugs are used, respectively [25].

Upon detection of a virus in the herpes group: HSV 1, 2, 6 types, CMV, EBV (PCR in oropharyngeal smear, saliva, blood — PCR or ELISA if IgM is to be detected), interferon-alpha drugs (in the form of sprays, drops — Genferon, Grippferon), as indicated, and systemic antiviral therapy (Acyclovir, Valvir, Famvir in tablet form or rectal insufflation (Viferon, Genferon, Kipferon)) are prescribed topically (systemically).

In the presence of mucosal edema and allergic reactions, antihistamines will be added to therapy, if ineffective — topical steroids, in insomnia — sedation.

For topical therapy (irrigation, inhalation, rinsing) there is a large selection of drugs with anti-infectious, anti-inflammatory and anesthetic (in the presence of pain) action, drugs of choice: Strepsils, Pharyngocept, chlorhexidine, Miramistin, Gramicidin S, Octenisept, Iodinol, spray — Inhalypt, Hexoral, Tantum Verde, Sialor or also "natural antiseptic" — calendula, chamomile, propolis (if there are no allergic reactions).

General recommendations — diet, clean air, treatment of comorbidities, dental caries, avoiding harmful habits (smoking, drinking alcohol, drinking hot drinks) play an important role in recurrent CP.

Given that inflammatory diseases of the nasal cavity are often present in chronic catarrhal pharyngitis, it is necessary to sanitize the nose, paranasal sinuses (elimination of purulent infection, elimination of the causes of nasal breathing disorders, sanation of lymphadenoid formations and primarily pharyngeal tonsils).

Attention should be paid to the general condition of the body, to exclude diseases of other organs and systems, the presence of allergies, some genetically determined dysmorphic oral cavity, nose and pharynx.

Thus, the treatment of chronic pharyngitis should be comprehensive. It is important to carry out therapy taking into account the type of inflammation caused by the pathogenic, opportunistic in high concentrations microflora in the layers of the mucous membrane, the virulence of which is supported by impaired trophism and a decreased local cellular and humoral immunity [31].

Based on this, the etiotropic treatment of chronic pharyngitis should be aimed at eliminating the pathogenic, as well as excess content of opportunistic microflora with the help of appropriate bactericidal (bacteriostatic) agents. Immunotropic drugs (Imudon, Licopid, Polyoxidonium, IRS, Ribomunyl, etc.) potentiate the action of "basic" drugs. Drugs that increase the overall resistance of the body (vitamin C, zinc preparations,

omega-3, probiotics containing lactobacilli, etc.) are of great importance in the treatment of chronic pharyngitis. The use of antiallergic, desensitizing, sedative, metabolic process normalizing agents, vitamin therapy, restoration of micronutrient deficiency play an important role in the preservation of homeostasis of the mucous membrane in the upper respiratory tract [13, 40].

Treatment of chronic pharyngitis exacerbations: topical therapy

The choice of the optimal drug is determined by the spectrum of its antimicrobial activity, the absence of allergenicity and toxic effect, i. e., the local administration of drugs with a wide range of antimicrobial activity in many cases is the method of choice.

Drugs used for topical treatment of CP can be divided into seven groups: topical antibiotics, antiseptics, antiviral drugs, immunocorrection drugs, local anesthetics, anti-inflammatory drugs, homeopathic remedies [1]. In uncomplicated CP, there is usually no need for systemic administration of antibiotics [9]. Currently, there is a tendency in the world to use topical drugs for relief of inflammatory processes in CP. This is due to the growing allergization of the population in most countries, a high percentage of side effects of systemic drugs and their low effect on inflammatory diseases of the pharynx [14].

Optimal for sore throat is the administration of drugs that have not only an antiseptic effect, but also can quickly relieve pain [5].

Typically, the composition of drugs for topical treatment of CP includes one or more antiseptics: Miramistin, gramidin S, chlorhexidine (be mindful of the toxicity of chlorhexidine, part of Antiangin, Drill, Sebidin, Eludril, and prevent their unrestricted and uncontrolled use by patients (especially children), Hexetidine (Hexoral), Benzydamine, Ambazon, thymol and its derivatives, alcohols, iodine, etc.), essential oils, less — antibiotics (Framycetin) or sulfonamides, deodorizing means, natural preservatives (plant extracts, bee products), synthesized nonspecific protection factors of the mucous membranes, the components of the microflora (bacterial lysates, ribosomes, common determinants of bacteria — glucosamuramyldipeptide — Licopid).

Topical treatment of CP is carried out in the form of rinses, inhalations. Drugs can be produced in the form of tablets, drops or lozenges (Hexalyse, Drill, Septolete, Pharyngocept, neo-angin, Strepsils plus). However, this form of drugs has a relatively low activity and their administration is limited to mild forms of the disease.

Prescription of several drugs is limited by their allergenicity and irritant effect. This group includes drugs containing iodine derivatives (Iodinol, Jox, Vicadin, Povidone-Iodine), propolis (Proposol), sulfonamides (Bicarmint, Inhalypt). Drugs containing plant antiseptics and essential oils are effective and harmless, but their administration is contraindicated in patients who are allergic to pollen (pollinosis), and the number of persons with pollinosis in some geographical areas is up to 20% in the population.

In the treatment of chronic pharyngitis a variety of rinses (chamomile, sage, decoction of oak bark, eucalyptus, Bicarmint, Octenisept, etc.), inhalations (alkaline, lysozyme, trypsin), lubrication (Lugol solution on glycerin, tannin-glycerin, Collargol, Protargol, Sialor, etc.), bacterial lysates (IRS, Imudon, Ribomunyl, etc.) are also widely used. The complex of therapeutic agents uses a number of homeopathic remedies (Engystol, Lymphomyazot, etc.) and herbal medicinal products (Rotocan), as well as methods of aromatherapy (fir, cedar, pine oils, there are domestic sprays of essential oils non-allergenic series — Latta-Bio) [43]. Thus, the main requirements for the drugs applied to the mucous membrane are:

- a wide range of antimicrobial action, preferably including antiviral and antimicrobial activity;
- no toxic effect;
- low rate of absorption from mucous membranes;
- low allergenicity;
- no irritant effect on the mucous membrane.

The use of systemic antibiotic therapy in chronic pharyngitis

The need for systemic administration of antibiotics in exacerbations of CP is due to the appearance of pathogenic microorganisms, for example, beta-hemolytic Streptococcus, signs of general intoxication with high temperature, combined bacterial-viral, fungal microflora.

Antibacterial therapy is usually prescribed taking into account the sensitivity to antibiotics, identified pathogenic microflora [26, 30, 34, 38, 41] for a culture of oropharyngeal smear. Effective drugs for CP are penicillins (but they most often cause allergic reactions, dysbiosis, increased growth of fungal microflora), and macrolides. For example, an effective drug for CP is clarithromycin (Binoclar, Klabax, Claricin, Klacid, Fromilid) administrated per os; this drug is active against many intracellular microorganisms, gram-positive and gram-negative bacteria [11, 15, 17, 18].

Physiotherapy for chronic pharyngitis

Physiotherapy methods are effective in the complex treatment of CP. The effect of most of them is based on dilation of peripheral vessels, redistribution of blood and lymph flow, increased tissue nutrition, stimulation of redox processes. Diathermy, quartz, UHF, magnetotherapy, mud therapy, electro- and phonophoresis with vitamins, iodide, basic drugs, hydrocortisone, helium-neon laser are the most commonly used [21, 29].

Complications of chronic pharyngitis

The most frequent concomitant conditions and diseases in recurrent CP are lymphadenopathy of cervical lymph nodes (in 80% of cases), chronic tonsillitis, conjunctivitis, otitis media, sinusitis, maxillar sinusitis, labial form of herpes virus infection, EBVI (Epstein-Barr virus infection), laryngitis, tracheitis, bronchitis, pneumonia, paratonsillar abscess (often caused by streptococcal infection). Severe systemic complications of CP in combination with chronic tonsillitis are [10] rheumatic fever, rheumatic heart disease, glomerulonephritis (often caused by gram-negative bacteria), hematuria, psoriasis, urticaria, insomnia, arthritis.

Immunity in chronic pharyngitis

In recurrent CP, in case of ineffective complex treatment prescribed by otorhinolaryngologists, patients consult immunologists. A number of authors noted the suppression of local immunity of the pharyngeal mucosa — decreased production of secretory immunoglobulin A in saliva. This feature is more often revealed in the hyperplastic process in the pharyngeal mucosa [12]. In the catarrhal form of CP, a decrease in phagocytosis [11] is detected.

The peroxidase activity of saliva (PAS) in different forms of CP (catarrhal, hyperplastic, atrophic) was evaluated, and its increase in the catarrhal form of CP and its decrease in the hyperplastic form were revealed. Using topical therapy, it is possible to restore PAS — to increase the initially low level of peroxidase activity, while reducing the rate of CP exacerbations [1].

Indicators of systemic immunity in CP do not change often: in 90% of cases, the levels of 4 classes of immunoglobulins A, M, G, E, lymphocyte subpopulation, phagocytic activity of neutrophils and monocytes in the blood are within the normal range. Interferon status in 70% of patients is impaired: with leukocyte stimulation — production of α- and γ-interferons is reduced. In this case, serum interferon content is normal. The immunologist can prescribe an examination to determine sensitivity to various immunostimulants via Interferon status test; taking into account the sensitivity, the treatment regimen with the inclusion of immunostimulants is assigned [5].

In order to restore local immunity in CP, drugs with effect targeted on immune system, also having an anti-inflammatory effect, are widely used. The most widely used immunostimulants in CP are Licopid (sublingually or orally), Polyoxidonium, lysozyme, Genferon, Grippferon (drugs containing recombinant α-interferon), Imudon, Ribomunyl, IRS-19 (the last three drugs contain bacterial lysates, ribosomes of bacterial cells), plant-derived immunomodulators (for example, Tonsilgon N has anti-inflammatory and antiseptic effect, including antiviral one, stimulates phagocytosis, it includes marshmallow root, chamomile flowers, horsetail grass, walnut leaves, yarrow grass, oak grass, dandelion grass).

Many years of experience in the use of immunostimulants in recurrent CP show that remission can be extended to 3–6 months or more, followed by exacerbation, i. e., immunotherapy in CP should be a course. The work of pathology professor V. P. Bykova convincingly demonstrates that prolonged

use of immune stimulants locally in diseases of the upper respiratory tract leads to the development of hyperplasia of lymphoid tissue in the nasopharynx, i. e., excessive stimulation of local immunity is not recommended [6].

New approaches to the assessment of recurrent CP etiopathogenesis

Gas chromatography — mass spectrometry (mass spectrometry of microbial markers (MSMM)) is a modern diagnostic method for CP. MSMM allows to detect 57 microorganisms (species-specific fatty acids, aldehydes) by the level of stable markers in the oropharyngeal smear, 2 hours after delivery of the sample to the laboratory: 7 species of cocci, 21 species of anaerobic bacteria, 9 species of actinobacteria, 3 species of enterobacteria, species of gram-negative bacteria, viruses (herpes, EBV, CMV), species of microscopic fungi (2 species — *Candida, Aspergillus spp.*). Microbiota determined by MSMM includes resident (constantly represented in the pharynx) and transient microorganisms (in healthy individuals their content in the pharynx is 0, and increases significantly in CP).

A feature of MSMM is the ability to detect microorganisms in the biofilm — in the "sleeping state", while the micro colonies can be protected by mucin, polysaccharide capsules.

This method was tested in Russian health care facilities for more than 20 years. In 2010, Rospotrebnadzor allowed its use as a new medical technology in the diagnosis (Resolution FS 2010 /038 dated 24.12.20110 "Assessment of the microenvironmental status of a person by chromatography — mass spectrometry"). However, to date, the highly informative method of MSMM is little known to otorhinolaryngologists, therapists and immunologists, and is rarely used in practice because of the complexity in the interpretation of the results.

In their work, I. A. Snimshikova and co-authors [24] examined 62 patients with recurrent CP using the method of MSMM. Below we present to your attention the results.

The total content of microorganisms in 91% of persons with CP was elevated (in 68% of persons — it was 6–15 times higher, in 23% — 2–5 times, in 9% — normal). These data indicate the need for antibiotic therapy: local or systemic (depending on the type of microorganisms, the degree of increase in their content, the presence of general intoxication).

Endotoxin level was elevated in 87% of patients: while in 24% of persons, the increase was considerable (11–50 times), in 28% — moderate (6–10 times), in 48% this indicator increased slightly (2–5 times). These results confirm the clinical observations that in case of recurrent CP, in most patients (72%) there are no signs of general intoxication, but there are constant complaints that reduce the quality of life.

The content of plasmalogen* (P) was reduced in 71% of patients. The level of P is significantly dropped in 28% of persons (11–100 times), moderately (6–10 times) — in 11%, in 61% of persons — in mild degree (2–5 times). Given that P is involved in cholesterol metabolism, it can be assumed that these patients may fall into the high risk group for lipid metabolism disorders. This assumption requires special research.

In 100% of patients with CP who were under observation, an increase in the content of several transient microorganisms which normally do not occur in oropharynx (or occur in trace amounts) was found (Fig. 1). These are 2 types of Clostridium (*Blautia coccoides, Clostridium difficile*), *Enterococcus spp., Peptostreptococcus (17642), Kingella spp., Campylobacter mucosalis, cytomegalovirus (CMV)*. New etiopathogenetically significant bacteria identified in CP are inhabitants of the gastrointestinal tract: all patients with CP who were under observation (62 people) had complaints on the gastrointestinal tract (flatulence, constipation, diarrhea, heartburn, belching). In 79% of patients, the content of Campylobacter (a microorganism that plays a role in the etiopathogenesis of gastric diseases, gastroesophageal disorders) was elevated, the detected changes

* Plasmalogen is aldehydogenic lipid, which is produced by microflora (Eubacteria, Bifidobacteria, Propionibacteria, Clostridia) in the norm, protects unsaturated fatty acids from oxidation, and regulates the release of cholesterol from the cells.

confirm the data described in the literature that GERD, chronic gastritis play an important role in the pathogenesis of recurrent CP [24].

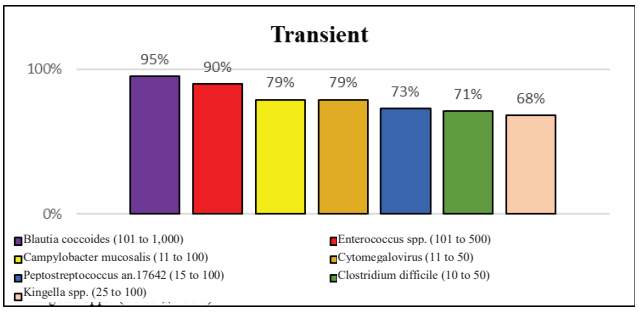

Figure 1. *Transient etiologically significant microorganisms in CP*

New etiopathogenetically significant microorganisms in CP detectable only using MSMM (in healthy individuals their content in oropharynx is 0). The vertical axis shows the percentage of persons with CP having elevated content of these microorganisms. The brackets indicate how many times their level increases.

The second group of etiologically significant microorganisms in CP (Fig. 2) includes 6 resident, opportunistic microorganisms constantly present in oropharynx. Their content increases in CP in 69–95% of patients, but the degree of increase is less significant than in microorganisms from group 1. This group includes both bacteria previously known in CP (strepto- and staphylococci) and new microorganisms (Clostridium, Entamoeba histolytica, Bacteroides fragilis, Bacillus cereus, Nocardia asteroides) identified only with the use of MSMM.

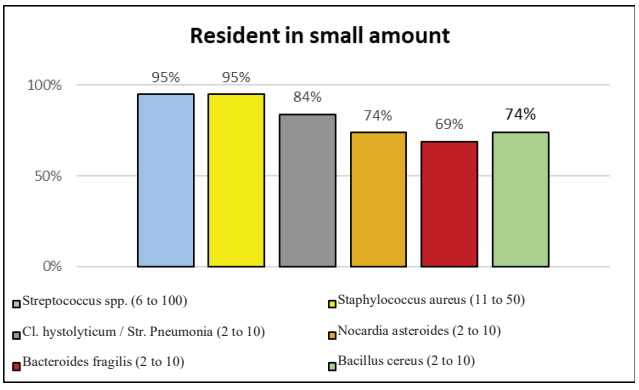

Figure 2. *Resident bacteria detected in the oropharynx in small amount in normal condition*

Etiopathogenetically significant in CP resident microorganisms are present in the oropharynx of healthy individuals in small quantities — up to 100×10^5 cells in 1 gram of sample. The symbols are the same as in Fig. 1.

The third group includes least etiopathogenetically significant in CP (Fig. 3) resident microorganisms found in healthy individuals in the oropharynx in large quantities. These are 5 opportunistic microorganisms, and the increase in their content in CP is moderate. Normally their level is high: ranges from 100 to 500×10^5 cells per 1 gram of sample.

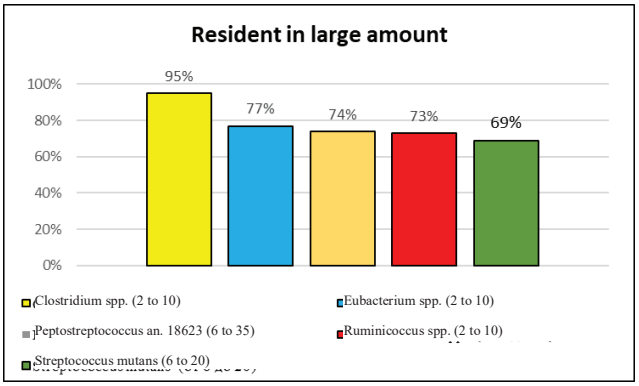

Figure 3. *Resident bacteria detected in the oropharynx in large amount in normal condition*

Using MSMM, a significant or moderate increase in the content of herpes, cytomegalovirus was detected in most (75%) patients: 21–100 times and 6–20 times, respectively, in 4% of individuals an increase in the level of these markers is small — 2–5 times, in a quarter of examined individuals (25%) virus content is normal. This observation indicates the important role of viruses of the herpes group in the etiopathogenesis of recurrent CP.

The level of *Candida spp.* was slightly elevated: in 45% of patients by 2–5 times, and in 55% it is within the normal range.

The content of normal microflora (*Lactobacillus spp., Bifidobacterium spp., Propionibacterium freudenreichii*), on average, was elevated in 71% of patients, indicating continued local resistance in patients with CP examined by the authors. Thus, the use of MSMM in CP allows to identify new etiopathogenic microorganisms, and on this basis to prescribe more effective therapy.

Main conclusions

1. Recurrent chronic pharyngitis (CP) is a chronic infectious and inflammatory process having complex etiopathogenesis, caused by a range of pathogenic factors.
2. The main factors supporting recurrent CP:
   2.1. etiologically significant microorganisms that acquire virulent properties and increased invasiveness by reducing the resistance, immunity of the patient;
   2.2. presence of concomitant chronic diseases in the patient, insufficiently compensated;
   2.3. effect of accompanying pathogenetically significant factors (occupational hazards, peculiarities of nutrition, etc.).
3. The new method — MSMM — is highly informative in CP and can be recommended for wide use in the diagnosis of upper respiratory tract disorders.
4. Through the use of MSMM in CP, new etiopathogenetically significant microorganisms were identified.
5. Based on the results of MSMM in CP, it is possible to develop more effective, personalized treatment regimens with the inclusion of immunotherapy.

Conflict of interests

The authors declare no conflict of interests.

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