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Current views on the functional status of the palatine tonsils in chronic tonsillitis and alternatives in treatment strategies (literature review)

Współczesne spojrzenie na stan funkcjonalny migdałków podniebiennych w przebiegu przewlekłego zapalenia migdałków oraz alternatywy w metodach leczenia (przegląd literatury)

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ABSTRACT:

Aim: This article presents an analysis of a literature review, which highlights the causal aspects of the development of chronic tonsillitis (CHT).

Material and method: The review contains statistical data on prevalence of this disease and high probability of local (tonsillar) and general (metatonsillar) complications development. Particular attention is paid to the issues of immunological reactivity of the macroorganism in conditions of chronic inflammation of the palatine tonsils (PT). The use of indicators of natural and acquired immunity in the diagnosis of CHT and in determining the direction of its treatment is justified. Data on the importance of biofilm in the genesis of chronic infectious processes, including PT, are systematized. In the etiology of inflammatory PT diseases, the development of their chronic course reflects the paramount importance of a wide range of microorganisms. The concept of biofilm, positioned by the authors as a specialized ecosystem that ensures maintenance of viability of the entire microbial association and preservation of its components, as well as a significant increase in the biomass of this population, has been developed.

Results: The study of biofilms revealed fundamental differences between planktonic and biofilm forms of microbiota existence, including differences in bacterial behavior, biochemical processes, biosynthesis of various substances, and exchange of genetic information. It is clear that biofilms can contribute to the transmission of resistance genes to antibiotics, as well as to other antimicrobial agents.

Conclusions: A study of the literature defines a new strategy for increasing the effectiveness of antimicrobial therapy for biofilm infections, which consists of the use of drugs from different pharmacotherapeutic groups acting to prevent biofilm formation and their morphofunctional destruction. There is experimental evidence that the use of drugs from these pharmaceutical groups can be effective in the complex treatment of diseases associated with biofilm formation.

KEYWORDS: biofilm, chronic tonsillitis, conservative treatment, immunological reactivity, surgical treatment

STRESZCZENIE:

Cel: W artykule przedstawiono analizę przeglądu literatury, w której zwrócono uwagę na aspekty przyczynowe rozwoju przewlekłego zapalenia migdałków.

Materiał i metody: Przegląd zawiera dane statystyczne dotyczące częstotliwości występowania tej choroby oraz prawdopodobieństwa rozwoju powikłań miejscowych (okołomigdałkowych) i ogólnych (pozamigdałkowych). Szczególną uwagę zwraca się na zagadnienia reaktywności immunologicznej makroorganizmu w warunkach przewlekłego zapalenia migdałków podniebiennych. Uzasadnione jest wykorzystanie wskaźników odporności naturalnej i nabytej w diagnostyce przewlekłego zapalenia migdałków oraz w określaniu kierunku jego leczenia. Usystematyzowano dane dotyczące znaczenia biofilmu w genezie

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przewlekłych procesów infekcyjnych, w tym migdałków podniebiennych. W etiologii chorób zapalnych migdałków podniebiennych, rozwoju ich przewlekłego przebiegu podkreśla się nadrzędne znaczenie szerokiej gamy mikroorganizmów. Powstała koncepcja biofilmu, który pozycjonowany jest przez autorów jako wyspecjalizowany ekosystem zapewniający utrzymanie żywotności całego związku drobnoustrojów oraz zachowanie jego składników, a także znaczny wzrost biomasy tej populacji.

Wyniki: Badania nad biofilmami ujawniły zasadnicze różnice pomiędzy planktonicznymi i biofilmowymi formami istnienia mikrobioty, w tym różnice w zachowaniu bakterii, procesach biochemicznych, biosyntezie różnych substancji oraz wymianie informacji genetycznej. Oczywiste jest, że biofilmy mogą ułatwiać przenoszenie genów oporności na antybiotyki, jak również inne środki przeciwdrobnoustrojowe.

Wnioski: Badanie literatury wyznacza nową strategię zwiększenia skuteczności terapii przeciwdrobnoustrojowej zakażeń biofilmowych, polegającej na zastosowaniu leków z różnych grup farmakoterapeutycznych, których działanie ma na celu zapobieganie powstawaniu biofilmów i ich morfofunkcyjną destrukcję. Istnieją potwierdzone doświadczalnie dane, że stosowanie leków z tych grup farmaceutycznych może być skuteczne w kompleksowym leczeniu chorób związanych z tworzeniem biofilmów.

SŁOWA KLUCZOWE: biofilm, górne drogi oddechowe, leczenie chirurgiczne, leczenie zachowawcze, przewlekłe zapalenie migdałków, reaktywność immunologiczna, szczepionki śluzówkowe

ABBREVIATIONS

AMPs – antimicrobial peptides
CHT – chronic tonsillitis
CICs – circulating immune complexes
DNA – deoxyribonucleic acid
ENT – ear, nose, and throat
EPS – a matrix or extracellular polymeric substance
ICD – International Classification of Diseases
IFN – interferon
Ig – immunoglobulin
IL – interleukin
LRT – lower respiratory tract
MALT – mucosa-associated lymphoid tissue
MIF – macrophage migration inhibitory factor
MRSA – methicillin-resistant *S. aureus*
MSSA – methicillin-sensitive *S. aureus*
MV – mucosal vaccines
NALT – nasopharyngeal-associated lymphoid tissue
PT – palatine tonsils
QS – Quorum sensing
sIg – secretory immunoglobulin
TE – tonsillectomy
TNF-α – tumor necrosis factor α
URT – upper respiratory tract
WHO – World Health Organization

RELEVANCE

Chronic tonsillitis (CHT) occupies one of the leading places in the structure of the general morbidity of ENT organs [1–4]. Chronic inflammation of the palatine tonsils (PT) is a multidisciplinary problem and is at the intersection of many medical specialties: otorhinolaryngology, rheumatology, cardiology, nephrology, allergology, immunology, etc. According to WHO, there are more than 100 diseases etiologically and pathogenetically associated with chronic inflammatory changes in PT. Attention to CHT is due not only to the widespread prevalence of this pathology, but also to the rapid chronicity of the inflammatory process and the high probability of developing local (tonsillar) and general (metatonsillar) complications. According to modern scientific sources, from 12.5% to 22.1% of the population suffer from CHT, which is from 22% to 40% among all chronic otolaryngological nosologies [5–7]. Despite the wide range of drugs of different pharmacological groups and dosage forms that are currently used in general and topical therapy of CHT, the frequency of chronic inflammation of the tonsils has increased by 1.5–1.8 in recent years and has no tendency to decrease [5, 8]. At the same time, the growth of purulent-inflammatory tonsillogenic and metatonsillar complications of CHT is noted [7–10].

Chronic tonsillitis is understood to be a disease of an infectious and allergic nature with local manifestations in the form of a persistent inflammatory response of the tonsil, which is morphologically expressed by simultaneous processes of alteration, exudation, and proliferation, and is associated with inhibition of nonspecific factors of natural resistance of the macroorganism. [11, 12]. In recent times, views on the etiology, pathogenesis, and development of adaptive reactions in conditions of chronic inflammation of the palatine tonsils have been changing. In this regard, in the scientific literature, the term "chronic" is proposed to be replaced by "recurrent" [13, 14]. However, researchers and practitioners in the present scientific publications use both the term "chronic" and "recurrent" almost with the same frequency [7, 15, 16]. Today in Ukraine, physicians apply the current ICD-10 classification and use the term "chronic tonsillitis" in their practice (J-35.0) [17].

THE ROLE OF THE LYMPHADENOID PHARYNGEAL RING IN SYSTEMIC AND LOCAL IMMUNITY REACTIONS DURING CHRONIC TONSILLITIS

PT belong to the nasopharyngeal-associated lymphoid tissue (NALT) that makes up the mucosal immune. The mucosa-ssociated lymphoid tissue (MALT) is the main link in the local defense of this biotope. Due to the contact of the antigen with the immunocompetent cells of PT, the immune response extends to all mucosal tissues of the body (the phenomenon of "mucosal solidarity"). Therefore, the current view is that the tonsils of the lymphadenoid ring (Tonsillar Ring) can participate in the formation of local immunity not only in the upper but also in the lower respiratory tract (URT and LRT), the initial parts of the digestive system and oral mucosa [18–20].

Systemic immunity reactions are implemented through the humoral and cellular immune system. The humoral link of immunity ensures the activation of antigen-specific B-lymphocytes, their transformation into plasma cells and production of antibodies (immunoglobulins) by the latter. The ability of plasma cells of PT to synthesize IgM, A, G, and D has been proved. Constant presence of sIgA and sIgM on the mucosal surface provides the first line of defense of the macroorganism. Under physiological normal conditions, the tonsils of the lymphadenoid pharyngeal ring have little effect on the overall level of antibody production in the body. However, under the conditions of inflammatory process development, the concentration of immunoglobulins of certain classes, mainly A and M, fluctuates significantly; an increase in titers of specific antibodies to the antigens of the main pathogens of CHT is observed.

Cellular immunity reactions are provided by various populations of lymphocytes: T-, B-, and NK- and their subpopulations, as well as cells capable of producing various types of cytokines. Depending on the phenotype of lymphocytes, their main subpopulations are distinguished: CD3+, CD4+, CD8+, CD19+, and CD16+-lymphocytes. Specifically, CD3+ is a surface marker specific for all cell subpopulations of T-lymphocytes. CD4+ – characteristic of helper T-cells; also present on monocytes, macrophages, dendritic cells. CD8+ – characteristic of suppressor and/or cytotoxic T-cells, NK cells (natural killer cells), mainly thymocytes. CD16+ – used along with CD56+ mainly for identifying NK-cells, is also present on macrophages, mast cells, neutrophils, and some T-cells. CD19+ – present on B cells, their precursors, follicular dendritic cells, considered to be the earliest marker of B-cell differentiation [21–23].

In PT, the following subpopulations of T-lymphocytes are distinguished according to the main functional differences: T-helpers, cytotoxic T-lymphocytes, T-suppressors, memory T-cells. T-helpers are lymphocytes that induce the activation, reproduction, and differentiation of other types of cells and play a regulatory role in the implementation of the immune response. T-helpers of the 1st type (Th1) and T-helpers of the 2nd type (Th2) are distinguished. Th1 produce mainly IL-2, interferon-γ (IFN-γ) and tumor necrosis factors (α and β), which activate components of cellular reactions. Th2 mainly synthesize IL-4, IL-5, IL-6, and IL-10, which leads to the activation of the humoral link of immunity. Functionally, Th1 and Th2 subpopulations have different vectors of influence and are antagonists to each other. However, these subpopulations are integral components of a single system.

Cytotoxic T-lymphocytes are lymphocytes endowed with effector functions and destroy virus-infected mutant and tumor cells. The suppressive function is characteristic of almost all T-lymphocytes. CD4+CD25+ T-lymphocytes are particularly active. These cells participate in the maintenance of immune tolerance and in limiting the immune response to endo- and exogenous antigens in order to prevent the occurrence of hyperergic reactions.

The effectiveness of the immune response depends on the levels of immune system mediators, cytokines. Cytokines are a group of biologically active regulatory peptides that ensure interaction between cells of the immune, hematopoietic, endocrine, and nervous systems. The main producers of cytokines are T-helpers and macrophages. The cytokine system currently includes about 200 individual polypeptide substances. All cytokines are divided into the following groups: interferons, colony-stimulating factors, chemokines, growth factors, and tumor necrosis factor. Cytokines are divided into pro-inflammatory and anti-inflammatory according to their functional activity. Pro-inflammatory cytokines include IL-1β, IL-2, IL-6, IL-8, GM-CSF, interferons and TNF-α. Anti-inflammatory cytokines are IL-4, IL-10, IL-13 and TFR-β. Cytokines, on the one hand, enhance the phenomena of alteration, destruction, and stimulate the synthesis of acute-phase proteins and oxidative stress. On the other hand, early development of adequate inflammatory processes promotes the restriction of the lesion focus, increase of barrier functions, regeneration, healing of tissue defect, and prevention of systemic complications. Anti-inflammatory cytokines inhibit inflammation; inhibit the synthesis of pro-inflammatory cytokines and the formation of highly active oxygen and nitrogen metabolites [24–28].

According to most authors, in chronic PT inflammation there is a suppression of the immunological reactivity of the macroorganism [29–31]. Reduced blood level of CD3+-, CD4+-lymphocytes and immunoregulatory index (CD4+/CD8+), with increased or normal concentration of CD8+-cells and elevated levels of circulating immune complexes (CICs), IL-4, TNF-α, INF-γ are observed in patients. At the same time, changes in the humoral response are characterized by a significant increase in IgM and IgG, decreased IgA titers in blood and oropharyngeal secretion, lysozyme deficiency, increased levels of proinflammatory cytokines (IL-1, TNF-α, MIF), activation of neutrophils and macrophages. According to other authors, there is a decrease in the quantitative indices of T and B lymphocytes in the blood, as well as a decrease in the concentration of IgM, IgG on the background of increased IgA titers [30, 32]. Colonization of mucosal PT by numerous species of microorganisms leads to sensitization of lymphocytes and determines the involvement of allergic reactions in the pathogenesis of chronic tonsillitis. Therefore, in the course of chronic inflammation of tonsils of the lymphadenoid ring, the number of cells-producers of IgE increases, and thus serum IgE increases as well. The use of indicators of natural and acquired immunity is a relevant criterion in the diagnostics of chronic tonsillitis and in determining the direction of treatment.

THE ROLE OF BIOFILMS IN THE DEVELOPMENT OF CHRONIC TONSILLITIS

The microflora of PT is composed of a wide range of microorganisms (viruses, bacteria, fungi), both in normal conditions and in pathological processes. Constant coexistence of numerous representatives of the microbial community, intermicrobial communication, as well as complex symbiotic relationships between the macroorganism and microbiota result in the formation of multi-species consortia of microorganisms – microbiocenoses. Multicomponent microbiocenoses are provided by the symbiosis of saprophytes-commensals, conditionally pathogenic and pathogenic microorganisms. The main representatives that are part of the bacterial-bacterial and fungal-bacterial microbial associations

in PT during their chronic inflammation are: *Streptococcus pyogenes, Staphylococcus aureus, Moraxella catarrhalis, Streptococcus pneumoniae, Hemophilus influenzae, Klebsiella pneumonia fungi of the genus Candida* [33, 34]. Peculiarities of interaction between associates of PT microbial groups can affect the form and course of the infectious process. At the same time, it should be noted that in the conditions of chronic inflammation of PT on the mucous membrane, microorganisms with pronounced signs of pathogenicity prevail due to the strengthening of their hemolytic, lecithinase, antilysozyme activities and the formation of antibiotic resistance [34]. The growth of the etiopathogenetic role of opportunistic and pathogenic microflora of the oropharynx (most often *S. aureus* and *St. pyogenes*) in the development of CHT, as well as tonsillogenic and metatonsillar complications may be due to a decrease in the immunological reactivity of the macroorganism.

The concept of the role of multispecies microbial biofilms in the development of acquired infections, including those of the ENT organs, remains relevant from the current point of view [35–38]. Both Gram-positive (*Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp.) and Gram-negative (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*) bacteriogenic and pathogenic, conditional associations may participate in biofilm formation. Hall-Stoodley et al. (2006) found biofilms in 92% of patients with chronic or recurrent middle ear disease, while Winther et al. (2009) found biofilms on the surface of removed adenoids in 88.8% of cases, and on the surface of PT in 70.8% [39, 40]. According to modern concepts, biofilm has a complex volumetric structural organization and is a form of existence of most microorganisms in the form of specifically organized communities characterized by intercellular communicative interactions. Biofilm formation is one of the main strategies to increase the survival of bacteria in an environment that is aggressive to it, including in the host. Preventing biofilm formation or destroying it is therefore a promising drug treatment for bacterial infectious diseases in humans.

Biofilms of different microbial communities share a common algorithm of formation and structural organization. The biofilm development cycle consists of several stages: the adhesion stage – primary sedimentation of cells into the substrate, monolayer formation, and biofilm maturation with the formation of all its structures. Biofilm development is completed by matrix rupture and dissemination of planktonic cells, followed by colonization of new surfaces. The main components of a biofilm are a surface membrane, a matrix or extracellular polymeric substance (matrix, EPS), and bacterial cells. The surface membrane, which provides insulation of the biofilm from the environment, consists of components of the cell membranes of the microbial community and has their characteristic properties. The proportion of EPS in the biofilm is approximately 85% and this is its basic structural component. The formation of the exopolymer matrix occurs through the synthesis of biopolymers by biofilm microorganisms. Typical matrix components are polysaccharides, proteins, and extracellular DNA. These compounds are highly hydrated, as 80–90% of the biofilm volume is water. The exopolysaccharides of the matrix have a structural function and prevent or inhibit the diffusion of substances unfavorable to it, such as antibiotics and disinfectants. Proteins play a role in intercellular contacts, implementation of the adhesion process in the cell-cell and cell-substrate direction, and contribute to the binding of polysaccharides in the biofilm structure. DNA is involved in horizontal gene transfer in the biofilm and cell-to-cell signaling. The matrix is divided by channels filled with water and also has cavities. Through the channels, nutrients are transported and convective oxygen flows from the outer to the inner parts of the biofilm, and bacterial cell metabolites are excreted. Thus, EPS, provides mechanical stability to the three-dimensional biopolymer structure of biofilms, regulates their ability to attach to surfaces, forms the internal environment, determines the activity of exchange processes between the environment and the biofilm, and provides increased resistance of biofilms to the action of antimicrobial agents and factors of nature. The composition of EPS depends on the micro-organism species and the environmental conditions [41–43].

When biofilm formation occurs in a colonized environment, the bacteria change from a planktonic form of existence to a microbial, sessile form, forming a biofilm. The sessile forms are characterized by reduced metabolism, slow population growth, enhanced adhesive properties, and the ability to aggregate into cell consortia. Film microorganisms are 100–1000 times less sensitive to most antibiotics than planktonic microorganisms. To date, it has been suggested that this resistance may be due to various mechanisms: 1) difficult penetration or inability of antibiotic to penetrate into the matrix; 2) binding and inactivation of antibiotic by polymers or proteins of matrix; 3) delayed division of bacteria in biofilm; 4) presence of a special subphenotype of bacterial cells – persister cells. Of these mechanisms, the existence of persister cells deserves special attention. The number of persistent cells in the microbial population does not exceed 1–3%. Persisters are formed during the stationary phase of growth; they are metabolically inert and acquire signs of antibiotic tolerance, which ensures the survival of the mother population in the presence of lethal factors for all cells. Persister tolerance is based on the ability of microbial cells to survive by eliminating basic biological processes; they are not characterized by active processes of growth and cell division. Maintenance of physiological quiescence is implemented with the participation of a group of specific genes encoding peptide synthesis, which ensure the reduction of biosynthetic and energetic activity of cells. At the same time, specific persister proteins exclude or block all antibiotic targets, and the cells acquire signs of multidrug resistance not only to antibiotics, but also to a number of compounds toxic to "normal" cells. Persistors play a special role in the development of chronic infectious diseases associated with film formation. The existence of persistors leads to prolonged treatment of microbial infections and forms the basis for the selection of multidrug-resistant microbial strains. Therefore, one of the areas of antimicrobial therapy for biofilm infections is the use of drugs capable of affecting energetic or metabolic processes in cells, as well as substances that do not require a metabolically active target [44–46].

The formation, growth, and differentiation of planktonic and sessile cells in biofilms are regulated at the population level through an intercellular communication mechanism called Quorum sensing (QS). The QS phenomenon is a special type of regulation of gene expression of microbes that depends on their population density.

This type of regulation of gene expression contains the necessary components: low-molecular-weight signal molecules autoinducers, which easily diffuse across the membrane of the bacterial cell, and a receptor regulatory protein with which the autoinducer binds. When a critical level of the bacterial population is reached, autoinducers accumulate to the necessary threshold value and interact with the corresponding regulatory proteins, causing a sharp activation of the expression of certain bacterial genes, in particular, the population regulation of virulence factor expression is provided [47, 48].

Consequently, using QS, microorganisms carry out intraspecific and interspecific communication, interact with higher eukaryotes, and ensure survival under unfavorable conditions, in particular, exposure to aggressive substances – antibiotics and disinfectants. Since QS systems are involved in the control of bacterial virulence and biofilm formation, QS inhibitors may be of pharmaceutical importance, and drugs directed against pathogenic bacteria are developed on their basis. Thus, modern understanding of the biology of the existence of microorganisms, their behavior as colonial-social organisms, and the mechanisms of adaptive reactions of the microorganism allow a different view of the processes underlying the long-term, persistent, and complicated course of chronic diseases. In this regard, state-of-the-art technologies are being developed to determine the etiology of the disease, the immunological reactivity of the macroorganism, and to carry out effective treatment [49–52].

CURRENT TRENDS IN THE SURGICAL AND CONSERVATIVE TREATMENT OF CHRONIC TONSILLITIS

The problem of improving the treatment of patients with CHT is still a hot topic for otolaryngologists and has been the subject of much debate. It is known that there is no single pathognomic symptom or series of symptoms unique to CHT. Therefore, the choice of therapeutic tactics is usually based on the patient's complaints, history, local objective changes, complications, and laboratory examination data. According to the authors, the use of modern immunological and molecular genetic studies will help to assess the functional status of the palatine tonsils and, accordingly, determine the direction of treatment: surgical or conservative.

The main surgical treatment for CHT is extracapsular tonsillectomy (TE). Currently, Paradise criteria are used in Europe and the USA to determine if TE is necessary, mainly in children. According to the Paradise criteria, a pediatric tonsillectomy is indicated if there have been 7 or more episodes of acute tonsillitis in the past year, or 5 or more episodes in the past 2 years, or 3 or more episodes in the past 3 consecutive years [53–55]. According to other researchers, the presence of paratonsillar abscess, metatonsillar complications, persistent carrier of β-hemolytic streptococcus group A, and increased serum antibody concentrations to the antigens of this pathogen are also indications for TE [10, 56, 57]. In the modern world, otorhinolaryngologists have a wide choice of different methods of TE, the differences of which are physical parameters, the frequency and volume of postoperative bleeding and other complications, and the speed of recovery. All TE methods are divided into "cold" and "hot". The "cold" method involves performing TE without using heat – a classic instrumental PT dissection (cold dissection). In this case, the surgical procedure is carried out in a standard way using surgical instruments under local or general anaesthesia. "Hot" methods include electrocautery, laser and radiofrequency methods, mono- and bipolar cautery (high-frequency electric current), ultrasonic scalpel (high-frequency ultrasound), infrared laser, cold-plasma coagulation, and argon-plasma coagulation [10, 58]. Classic instrumental PT dissection is the most common method of performing TE in the world [14, 58]. During standard instrumental surgery (cold dissection), primary and secondary postoperative bleeding occurred in 0.8% of cases, performing TE with mono- and bipolar coagulation for hemostasis reduced the risk of bleeding to 0.5%, and the use of bipolar diathermal cautery to 0.4%. When cold plasma coblation TE was used, postoperative bleeding was observed in 1% of cases [10]. According to American researchers, the use of a coblation device (coblator) caused mucosal burns, mainly of the first degree, in 42% of the operated patients, with this complication occurring in 25% of cases when using a monopolar cautery [59]. A complication such as uvula edema occurred more frequently after conventional TE (32%) than after coblative TE (14%) [4]. A study of the distant results of the post-transplantation TE demonstrates the effectiveness of all of these techniques [14, 58, 60, 61]. In recent decades, there has been a decrease in the number of performed TE's worldwide [62–65]. This trend is assessed by scientists in different ways. Practitioners believe that the decrease in the number of TE and predominance of conservative methods in the therapeutic tactics of CHT leads to an increase in the incidence, primarily, of local purulent-inflammatory complications, as well as metatonsillar complications [66, 67]. In the absence of indications for surgical treatment of CHT, the prescription of conservative treatment is recommended for patients. Conservative treatment is aimed at eradication and/or decolonization of the pathogen, improvement of functional activity of PT, regression of subjective and objective signs of the disease, prevention of complications, reduction of exacerbations, and improvement of quality of life of patients. Systemic antibiotic therapy is indicated only for the treatment of exacerbation episodes of CHT.

During remission, the most common conservative treatment for CHT is local sanation. To achieve this goal, it is possible to use washing the crypts of the PT with antiseptic solutions [68, 69]. Application of this method provides removal of desquamated epithelium cells, numerous microorganisms and products of their vital activity, leukocytes, food residues, etc. from the cripta of PT. The antimicrobial action of antiseptic solutions provides eradication and decolonization of mainly planktonic forms of the major CHT pathogens. However, the effect of antimicrobials on the microorganisms that make up bacterial biofilms remains a reactive and debatable issue.

An extensive range of agents from various pharmacological groups has been shown to have an antimicrobial effect on planktonic and sessile forms of micro-organisms. These include mucolytics, non-steroidal anti-inflammatory, antineoplastic, anthelmintic, and hypolipidemic agents. The antibiofilm activity of the mucolytic agent N-acetylcysteine has been proven in numerous studies [70–72]. The mechanism of the antibiofilm activity of N-acetylcysteine is the disruption of exopolysaccharide synthesis of the biofilm matrix.

The suppression of *Streptococcus pneumoniae and Haemophilus influenzae* adhesion to oropharyngeal epithelial cells under the influence of N-acetylcysteine has been proved, the sensitivity of methicillin-resistant and methicillin-sensitive strains of *Staphylococcus epidermidis* to it has also been established [70, 73].

Some non-steroidal anti-inflammatory drugs also exhibit antibiofilm activity. Studies have shown that salicylic acid and its derivatives inhibit *P. aeruginosa* mobility and film-forming ability. The use of salicylic acid in therapeutic doses prevents adhesion of different types of bacteria, and with increasing of its concentration inhibition of adhesin synthesis of *S. epidermidis* occurs [72, 74]. The combined use of acetylsalicylic acid and N-acetylcysteine minimize the formation of biofilm on the surface of the mucosa of the palatine tonsils in chronic tonsillitis [75]. Diclofenac sodium and ibuprofen also demonstrate antibiofilm activity [76, 77].

The antineoplastic agent 5-fluorouracil is characterized by antimicrobial activity against *S. aureus* and *S. epidermidis* [78].

The hypolipidemic drug simvastatin inhibits adhesion, production of exopolysaccharides and film formation of MSSA and MRSA strains, and also exhibits antibiofilm activity against *P. aeruginosa*, *Candida* spp. and *Cryptococcus* spp. [51, 79].

Antimicrobial peptides (AMPs) are considered an attractive alternative to antimicrobials in modern medical science. The advantages of these agents are high selectivity, powerful bactericidal action and a broad spectrum of activity, low frequency of bacterial resistance, and low toxicity to macroorganismal cells. Antibiofilm activity of AMP is realized in low concentrations, associated with inhibition of adhesion and mobility of microorganisms, and QS disruption [80]. Simultaneous use of AMP and antibiotics is characterized by a synergistic effect against biofilms formed by MRSA [81].

The benefits of the use of bacteriophages in the treatment of biofilm infections are discussed. Bacteriophages are viruses that can infect bacteria and cause their destruction (lysis). The quantitative reduction of bacterial cells by bacteriophages leads to a reduction in biofilm production. Scientific sources mention the influence of bacteriophages on QS-systems, which results in triggering lysis cycle in response to certain chemical signals [80, 82]. Bacteriophages are highly specific and do not inhibit normal microflora, can be used by pregnant women and children, stimulate humoral and cellular links of immunity, have no antigenic, toxic and teratogenic properties, can be effective as monotherapy, as well as in combination with antibiotics and probiotics [82, 83]. Further development and production of dosage forms of bacteriophages for immediate use (sprays, creams, applicators) are promising.

Probiotics are considered to be an effective treatment for biofilm-associated diseases. Prokaryotic probiotics (representatives of *genera Lactobacillus*, *Bacillus*), neutralize toxins and harmful to the macroorganism metabolites, as well as damage pathogen-specific QS [84–87]. Bacteriocins, enzymes, and other biologically active substances produced by probiotic microorganisms possess antagonistic activity against pathogenic and conditionally pathogenic microorganisms and open up additional possibilities in the fight against polyresistant bacterial strains organized into biofilm copepods.

Effective antimicrobials that affect planktonic and sessile bacteria in biofilms include essential oils. They have the ability to disrupt bacterial cell membranes and prevent bacteria from adhering to the surface of epithelial cells. Various essential oils (juniper oil, eucalyptus oil, peppermint oil, cajaput oil, etc.) are widely used in the treatment of URT infections by inhalation. A more pronounced antimicrobial effect of essential oils is observed when they are used in combination. It is suggested that the high antibacterial and antibiofilm activity of essential oils in the composition can be explained by their synergistic action [35, 88].

The regression of the subjective and objective symptoms of CHT and permanent remission of the disease can also be achieved by activation of the nonspecific and specific immune response. For this purpose, it is advisable to administer mucosal vaccines (MVs) in conservative treatment of CHT. MV contain microbial lysates derived from fragments of cell walls of microorganisms. Their use in clinical practice helps to stimulate high levels of specific antibody production. Strengthening of nonspecific immune response occurs due to activation of dendritic cells, macrophages, neutrophils, and Nk-cells, as well as induction of cell lysis and phagocytosis due to increased adhesion of macrophages on bacterial cells [89, 90]. Therefore, MV should also be used in other chronic inflammatory diseases of URT and for the prevention of their exacerbations.

CONCLUSIONS

Thus, the review of the current state of the problem of CHT reflects the important role of PT in the development of immunological reactions both under physiological conditions and in chronic inflammation. Diagnosis of CHT today should be based on the results of the culture method and the study of indicators of the immune and cytokine status of patients. The current understanding of the existence of microorganisms in biofilms allows a new understanding of the development and course of the chronic infection process. Analysis of the literature suggests a new strategy to increase the efficiency of antimicrobial therapy of biofilm infections, which consists of the use of drugs of different pharmacotherapeutic groups that destroy extracellular matrix or increase its permeability, affecting QS-system, metabolically inactive cells or causing their reversion to active one. Understanding the nature of biofilm determines the development of new approaches in chronic tonsillitis therapy and patient management algorithms.

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