

About authors:

Nartokova Aminat Sultan-Khamidovna, Assistant of the Department of Oncology and Radiation Therapy with a Course of Additional Professional Training, oncologist of the Department of Tumors of the Breast, Skin, Bones and Soft Tissues № 2; tel.: +79288171712; e-mail: aminatjolova@gmail.com; <https://orcid.org/0000-0001-9426-4434>

Koychuev Arsen Askерович, MD, DMSc, Associate Professor, Head of the Department, Deputy Chief Physician; tel.: +79288262499; e-mail: koichuev26@mail.com; <https://orcid.org/0000-0003-2856-1056>

Sorokina Nina Valerievna, oncologist; tel.: +79187707810; e-mail: nita-s@mail.ru; <https://orcid.org/0009-0003-9473-5832>

Chumakov Petr Ilyich, MD, DMSc, Professor, Head of the Department of Urology; tel.: 89054983128; e-mail: p-chumakov@mail.ru; <https://orcid.org/0000-0002-6566-6087>

Khatsiev Bekhan Bayalovich, DMSc, Associate Professor of the Department of Surgery and Endosurgery with a Course in Vascular Surgery and Angiology; tel.: +79283211335; e-mail: bkhatiev@yandex.ru; <https://orcid.org/0000-0002-3694-5781>

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DIAGNOSTICS AND ANTIBACTERIAL THERAPY OF STREPTOCOCCUS-ASSOCIATED TONSILLITIS

A. V. Dengina¹, V. P. Karpov^{2,3}, V. A. Baturin², L. S. Badiryan²

¹ Regional Children's Clinical Hospital, Stavropol, Russian Federation

² Stavropol State Medical University, Russian Federation

³ City Clinical Hospital № 3, Stavropol, Russian Federation

ДИАГНОСТИКА И АНТИБАКТЕРИАЛЬНАЯ ТЕРАПИЯ СРЕПТОКОКК-АССОЦИИРОВАННЫХ ТОНЗИЛЛИТОВ

А. В. Деньгина¹, В. П. Карпов^{2,3}, В. А. Батурин², Л. С. Бадириян²

¹ Краевая детская клиническая больница, Ставрополь, Российская Федерация

² Ставропольский государственный медицинский университет, Российская Федерация

³ Городская клиническая больница № 3, Ставрополь, Российская Федерация

The sensitivity of Group A β -hemolytic *Streptococcus pyogenes* (GABHS) to various antibacterial drugs in patients with chronic tonsillitis for 2019–2023 was studied. Six hundred thirty-six medical records of patients with this pathology and a positive microbiological examination of a smear from the pharyngeal mucosa for GABHS, who underwent treatment and assessment in 2019, 2021, and 2023, were analyzed. It was found that the sensitivity of *S. pyogenes* to penicillin antibiotics remains at the level of 100 %. Of the «reserve» antibiotics, doxycycline remains highly sensitive. There is increased resistance to second-line antibacterial drugs used in treating chronic tonsillitis in patients intolerant to penicillin antibiotics, primarily macrolides and fluoroquinolones. Thus, amoxicillin is the starting antibiotic therapy in patients with chronic tonsillitis caused by *S. pyogenes*. For patients with a history of allergies to penicillin antibiotics, to prescribe effective treatment, it is necessary to conduct a microbiological examination of a smear from the pharyngeal mucosa to determine the sensitivity of *S. pyogenes* to «reserve» antibacterial drugs.

Keywords: group A β -hemolytic *Streptococcus* (GABHS), *Streptococcus pyogenes*, antibacterial therapy, antibiotic resistance, chronic tonsillitis

Изучена чувствительность *Streptococcus pyogenes* (БГСА) к различным антибактериальным препаратам у пациентов с хроническим тонзиллитом за период 2019–2023 гг. Были проанализированы 636 медицинских карт пациентов с положительным микробиологическим исследованием мазка со слизистой глотки на БГСА, проходивших лечение и обследование в 2019, 2021 и 2023 гг. Установлено, что чувствительность *S. pyogenes* к антибиотикам пенициллинового ряда сохраняется на уровне 100 %. Из «резервных» антибиотиков высокая чувствительность остается у доксициклина. К антибактериальным препаратам «второй» линии, применяемым при лечении хронического тонзиллита у пациентов с непереносимостью пенициллиновых антибиотиков, в первую очередь к макролидам и фторхинолонам, отмечается повышение резистентности. Таким образом, стартовой антибактериальной терапией у пациентов с хроническим тонзиллитом, вызванным *S. pyogenes*, является амоксициллин. Пациентам, имеющим в анамнезе аллергию на антибиотики пенициллинового ряда, с целью назначения эффективной терапии необходимо проведение микробиологического исследования мазка со слизистой глотки для определения чувствительности *S. pyogenes* к «резервным» антибактериальным препаратам.

Ключевые слова: β -гемолитический стрептококк группы А, *Streptococcus pyogenes*, антибактериальная терапия, антибиотикорезистентность, хронический тонзиллит

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CT – chronic tonsillitis
GABHS – group A β -hemolytic *Streptococcus*

PANDAS – Pediatric Autoimmune Neuropsychiatric Disorders
Associated with Streptococcal infections

One of the pressing health problems is the progressive increase in forms of microorganisms resistant to antibacterial agents [1]. The problem of resistance today is considered from the standpoint of national security [2]. In 2019, the President of the Russian Federation issued Decree № 97 of March 11, 2019, «On the Fundamentals of State Policy of the Russian Federation in the field of ensuring chemical and biological safety for the period until 2025 and beyond», which denotes biological threats. This decree mentions among biological threats «...a disruption of the normal human microbiota, leading to the occurrence of diseases and their spread; lack of specific immunity to certain infections controlled using specific prophylaxis; spread of antimicrobial resistance, increasing epidemiological significance opportunistic microorganisms...» The issues of irrational antibiotic therapy and, as a consequence, the spread of antibiotic-resistant microorganisms are acute in diseases of the ENT organs, especially chronic tonsillitis caused by group A β -hemolytic *Streptococcus* (GABHS). The growth of resistant strains of microorganisms after massive and widespread antibacterial therapy during the Covid-19 pandemic, as well as the increased number of streptococcal tonsillitis and streptococcal-associated metatonsillar diseases, force a new assessment of the role of *St. pyogenes* in the occurrence and course of chronic tonsillitis and, as a result, to develop rational antibacterial tactics for this disease.

An essential link in the pathogenesis of chronic tonsillitis is the immunodeficiency state of the body, leading to changes in the phagocytic and antigen-recognizing functions of tissue macrophages, which contribute to the infectious and allergic process. Nevertheless, contagious agents' role in chemotherapy's pathogenesis is quite significant. Thus, the main etiological factor of this disease is group A β -hemolytic *Streptococcus* [3, 4]. According to G. S. Maltseva [3], chronic inflammation of the tonsils activates autoimmune reactions and contributes to autoimmune diseases. Chronic tonsillitis causes pathological changes in other organs and systems through the direct penetration of microorganisms and their metabolic products into the vascular bed and through the autoimmune and neuro-reflex pathways through the influence of auto-antibodies [3].

The connection between chronic tonsillitis and post-streptococcal infections such as rheumatism, myocarditis, glomerulonephritis, and infectious nonspecific polyarthritis has been well studied. Also, in recent years, a lot of data has appeared on the connection between chronic tonsillitis and other autoimmune diseases: Ig-A nephropathy (Berge's disease) – kidney disease, Pustulosis palmaris et plantaris (skin disease), circle cell disease (blood disease) and PANDAS syndrome.

The purpose of the study is to compare the sensitivity of *S. pyogenes* to antibacterial drugs in patients with exacerbation of chronic tonsillitis, including those complicated by peritonsillar abscesses.

Material and Methods. Six hundred thirty-six outpatient and inpatient records of patients with chronic tonsillitis, including those complicated by peritonsillar abscesses, undergoing examination and treatment at the City Clinical Hospital № 3 (Stavropol) from 2019 until 2023, were analyzed. Patients over 18 years of age were included in the study. All patients in the study group had clinical signs of exacerbation of chronic tonsillitis complicated by peritonsillar abscesses, were examined by an otorhinolaryngologist, and underwent microbiological examination of a swab from the pharyngeal mucosa to determine *S. pyogenes* and its sensitivity to antibacterial drugs. Two groups of patients were formed and divided depending on the time of examination. Group 1 included 100 patients with exacerbation of chronic tonsillitis and with a positive microbiological test for *S. pyogenes* who were examined in 2019, Group 2 included 138 patients who were reviewed in 2021, and Group 3 included 398 patients who were examined in 2023.

Statistical analysis was carried out using the StatTech program 3.0.9. (Stattech LLC, Russia). Comparison of percentages in the study of four-field contingency tables was performed using the Pearson χ^2 -test, Fisher's exact test. A comparison of percentages was performed using the Pearson χ^2 -test to analyze multifield contingency tables.

Results and Discussion. The obtained data on the sensitivity of *S. pyogenes* to various groups of antibacterial drugs is presented in Table 1. The sensitivity of *S. pyogenes* to penicillin antibacterial drugs remains 100 %, but resistance to «reserve» antibiotics is increasing: fluoroquinolones, macrolides, and lincosamides. The data showed a statistically significant increase in resistant strains of group A β -hemolytic *Streptococcus* to levofloxacin and moxifloxacin. Susceptibility of *S. pyogenes* to levofloxacin in 2019. was 100 % (100), and 2021 and 2023 were 89 % (122) and 86 % (342), respectively ($p < 0.001$). The sensitivity of GABHS to moxifloxacin decreased only in 2023: from 100 % in 2019 and 2021 to 95 % (378) in 2023; statistically significant differences were found between Groups 2 (100 % sensitivity in 2021) and Group 3 (95 % in 2023) ($p = 0.003$, method used). Particularly alarming is the growth of antibiotic-resistant strains of GABHS to macrolides, which are approved for use in childhood. Azithromycin sensitivity decreased statistically significantly from 93 % (93) in 2019, 78 % (107) in 2021, to 52 % (207) in 2023 ($p < 0.001$). The sensitivity of *S. pyogenes* at 100 % in 2019–2023 was preserved only to doxycycline. Probably, the reasons for the growth of resistant strains of *S. pyogenes* resulted from a multiple increase in the prescriptions of macrolides and fluoroquinolones, primarily azithromycin and levofloxacin, during the COVID-19 pandemic; as well as the unreasonable prescription of antibacterial therapy for tonsillopharyngitis of viral etiology. This statement is confirmed by other studies [5], showing a decrease in opportunistic microflora's sensitivity (pneumococci, streptococci) to respiratory fluoroquinolones and macrolides. The growth of resistant strains of GABHS to «reserve» antibiotics in the «post-COVID» period has also been demonstrated.

Table 1

Sensitivity of *Streptococcus pyogenes* to antibacterial drugs

Antibacterial drug	Group 1 (n=100)	Group 2 (n=138)	Group 3 (n=398)
Benzyl-penicillin	100 %	100 %	100 %
Levofloxacin	100 %	89 %	86 %
Moxifloxacin	100 %	100 %	95,2 %
Azithromycin	93 %	78 %	52 %
Clindamycin	97 %	78 %	64 %
Doxycycline	100 %	100 %	100 %
Rifampicin	100 %	100 %	98 %
Linezolid	100 %	100 %	100 %

To determine the correct antibacterial tactics for tonsillitis treatment, it is necessary to carry out a differential diagnosis of the viral and bacterial etiology of the disease. The «gold» standard for diagnosing GABHS infection of the upper respiratory tract is bacteriological examination of infected pharyngeal mucosa with determination of the sensitivity of the identified pathogen to antimicrobial drugs. Considering that the turnaround time for this study is several days and requires a specialized laboratory, clinicians resort to alternative diagnostic methods – rapid tests and clinical diagnostic scales. To diagnose GABHS tonsillitis, clinicians should use the Centor and modified W. McIsaac scales (Table 2) [6]. However, according to some literature data [7, 8], the Centor and McIsaac indicators are equally ineffective for assessing GABHS tonsillopharyngitis. A. Kanagasabai et al. [8], in a meta-analysis, showed that when using these scales, many cases of streptococcal infection of the upper respiratory tract were missed, and, at the same time, there were many false-positive results, which led to excessive prescription of antibacterial drugs.

Table 2

W. McIsaac scales for the diagnosis of GABHS tonsillitis/pharyngitis

Criteria	Grade
Grade Body temperature over 38 °C	1 point
No cough	1 point
Enlarged and painful cervical lymph nodes	1 point
Under 15 years	1 point
15–44 years	0 point
45 years or more	–1 point

Note. Algorithm for prescribing antibacterial therapy (ABT) according to the W. McIsaac scale: 0–1 point – ABT is not indicated; 2 points – ABT at the doctor's discretion; 3–5 points – ABT is indicated.

Also, to diagnose GABHS tonsillitis, express immunochromatographic studies are carried out: if the express test is positive, the prescription of a penicillin antibiotic is indicated [9]. Such methods have high specificity and sensitivity to *S. pyogenes* and help in the differential diagnosis of upper respiratory tract infections of viral and streptococcal etiology [10]. Unfortunately, these tests do not allow determining the sensitivity of GABHS to «reserve» antibiotics, which are needed in patients intolerant to penicillin antibiotics [11]. Thus, the first line of antibacterial therapy is amoxicillin for infectious diseases of the tonsils caused by *St. pyogenes*. But, according to the literature [12–14], 10 % of the population had an allergy to penicillins. In patients allergic to penicillin antibiotics, an empirical prescription of macrolide antibiotics, as is the case in modern clinical practice, may be ineffective in treating GABHS infection.

Conclusion. The essence of the mentioned above boils down to the fact that patients with a clinical picture of GABHS-tonsillitis and with intolerance to penicillin antibiotics need a timely prescription of a microbiological test – a smear from the pharyngeal mucosa with determination of sensitivity to antibacterial drugs to prescribe effective antibacterial therapy, which may help to avoid streptococcus-associated complications.

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About authors:

Dengina Anzhelika Valerievna, otorhinolaryngologist of the Department of Otorhinolaryngology;
tel.: +79283271069; e-mail: lika.dengina@gmail.com; <https://orcid.org/0009-0008-1972-4013>

Karpov Vladimir Pavlovich, MD, Professor, Head of the Department;
tel.: +79624427047; e-mail: Karpov_Vladimir_@mail.ru; <https://orcid.org/0000-0001-8508-874X>

Baturin Vladimir Aleksandrovich, MD, Professor, Head of the Department
of Clinical Pharmacology, Allergology and Immunology;
tel.: +79614650167; e-mail: Prof.baturin@gmail.com; <https://orcid.org/0000-0002-6892-3552>

Badiryan Levon Sargisovich, student;
tel.: +79614654769; e-mail: lev.lev.10000@mail.ru; <https://orcid.org/0009-0005-7543-3489>

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SIGNIFICANT FIBROSIS IN CHRONIC LIVER DISEASES: POSSIBILITIES OF NONINVASIVE SCREENING

P. V. Koroy, T. R. Dudov, V. J. Sarithala, A. V. Yagoda

Stavropol State Medical University, Russian Federation

ВЫРАЖЕННЫЙ ФИБРОЗ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ПЕЧЕНИ: ВОЗМОЖНОСТИ НЕИНВАЗИВНОГО СКРИНИНГА

П. В. Корой, Т. Р. Дудов, В. Д. Саритхала, А. В. Ягода

Ставропольский государственный медицинский университет,
Российская Федерация

The investigation aimed to study the prognostic significance of clinical and laboratory parameters, including markers of the matrix metalloproteinases (MMP) system, for the detection of significant fibrosis (F2–4) in chronic liver diseases (CLD). Seventy-six patients with CLD of viral or alcoholic etiology aged 18 to 64 years were examined. Fibrosis F0–1 was found in 36.8 % of cases, and fibrosis F2–4 – in 63.2 %. Enzyme-linked immunosorbent assay was used to determine the blood levels of MMP-1, MMP-9, and tissue inhibitors of matrix metalloproteinases-1 (TIMP-1). The ratio TIMP-1/MMP-1, TIMP-1/MMP-9 was calculated. Increased risk of fibrosis F2–4 was associated with parameters of liver stiffness ≥ 7.3 kPa, gamma-glutamyltranspeptidase ≥ 37 u/l, aspartate aminotransferase ≥ 53 u/l, ESR ≥ 8 mm/h, platelets $\leq 187 \times 10^9$ /l, age ≥ 45 years, alanine aminotransferase ≥ 68 u/l, TIMP-1/MMP-1 ≥ 36.4 , albumin ≤ 43 g/l, total bilirubin ≥ 16 μ mol/l, TIMP-1 ≥ 501 ng/ml, international normalized ratio ≥ 1.08 , alkaline phosphatase ≥ 112 u/l, with the presence of moderate/severe cytolysis. According to multivariate logistic regression, liver fibrosis F2–4 was associated with blood levels of TIMP-1 and platelets, values of ESR. The combination of these parameters had a sensitivity of 70.8 % and a specificity of 100 % in the prediction of fibrosis F2–4. Thus, the levels of TIMP-1 and platelets in the blood and ESR are independent risk factors for significant fibrosis in CLD due to their participation in hepatic fibrogenesis.

Keywords: chronic liver diseases, significant liver fibrosis, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, platelets, erythrocyte sedimentation rate, screening

В работе определялась прогностическая значимость ряда клинко-лабораторных показателей, в том числе маркеров системы матриксных металлопротеиназ (ММП), для выявления выраженного фиброза (F2–4) при хронических заболеваниях печени (ХЗП). Обследовано 76 больных ХЗП вирусной или алкогольной этиологии в возрасте от 18 до 64 лет. Фиброз F0–1 встречался в 36,8 % случаев, фиброз F2–4 – в 63,2 %. Методом иммуноферментного анализа определяли содержание в крови ММП-1, ММП-9, тканевого ингибитора матриксных металлопротеиназ-1 (ТИМП-1), рассчитывали соотношение ТИМП-1/ММП-1, ТИМП-1/ММП-9. Увеличенный риск фиброза F2–4 был связан с показателями жесткости печени $\geq 7,3$ кПа, γ -глутамилтранспептидазы ≥ 37 ед/л, аспарагиновой аминотрансферазы ≥ 53 ед/л, СОЭ ≥ 8 мм/час, тромбоцитов $\leq 187 \times 10^9$ /л, возраста ≥ 45 лет, аланиновой аминотрансферазы ≥ 68 ед/л, ТИМП-1/ММП-1 $\geq 36,4$, альбумина ≤ 43 г/л, общего билирубина ≥ 16 мкмоль/л, ТИМП-1 ≥ 501 нг/мл, международного нормализованного отношения $\geq 1,08$, щелочной фосфатазы ≥ 112 ед/л, с наличием умеренного/высокого цитолиза.