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Comparative analysis of *Streptococcus pyogenes* sensitivity and effectiveness of antibacterial therapy in chronic tonsillitis

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Abstract

Background. The rise in antibiotic resistance of *Streptococcus pyogenes* in chronic tonsillitis remains a global issue, exacerbated by irrational use of antibacterial drugs, low patient adherence to therapy, and the spread of resistant strains. The discrepancy between the relatively high *in vitro* sensitivity of microorganisms and the reduced clinical efficacy of drugs *in vivo* is of particular concern and requires an in-depth analysis of the causes of such disparities.

Aim. The study aims to evaluate the efficacy of various groups of antibacterial drugs *in vitro* and *in vivo* used to treat chronic tonsillitis during exacerbations.

Material and methods. Based on outpatient records and microbiological studies, a group of patients was identified in whom *S. pyogenes* was the primary significant factor in the development of chronic tonsillitis. The sensitivity of the pathogen to commonly used antibacterial drugs was assessed using the disk-diffusion method. Clinical efficacy of antibiotic therapy was evaluated based on objective criteria. Additionally, isolates of *S. pyogenes* co-incubated with antibacterial agents were analyzed using Raman spectroscopy.

Results. The analysis revealed discrepancies between in vitro disk-diffusion data and clinical outcomes. According to the disk-diffusion test, 87.6% of patients showed sensitivity to semi-synthetic penicillins, yet incomplete or absent clinical efficacy was observed in 28.2% of cases. Slightly better results were obtained with inhibitor-protected penicillins. Macrolides, demonstrating 88.5% efficacy *in vitro*, failed to achieve full therapeutic effects in 26.6% of patients. Comparable results were observed with cephalosporins. The lowest *in vitro* sensitivity of *S. pyogenes* was noted for fluoroquinolones, leading to inadequate clinical efficacy in 28.0% of patients. Raman spectroscopy enabled the assessment of sensitivity to one of the most frequently used antibacterial agents.

Conclusions. The significant gap between laboratory and clinical data is attributed not only to potential antibiotic resistance mechanisms (which are also discussed) but also to the influence of internal factors that must be considered when selecting etiotropic therapy for chronic tonsillitis during exacerbations.

Keywords: chronic tonsillitis, antibiotic resistance, clinical efficacy, Raman spectroscopy.

Conflict of interest: nothing to disclose.

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Сравнительный анализ чувствительности *Streptococcus pyogenes* и эффективности антибактериальной терапии при хроническом тонзиллите

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Аннотация

Обоснование. Рост антибиотикорезистентности *Streptococcus pyogenes* при хроническом тонзиллите остается глобальной проблемой, усугубляемой нерациональным использованием антибактериальных препаратов, низкой приверженностью пациентов к терапии и распространением устойчивых штаммов. Особую тревогу вызывает противоречие между относительно высокой чувствительностью микроорганизмов *in vitro* и сниженной клинической эффективностью препаратов *in vivo*, что требует углубленного анализа причин таких расхождений.

Цель. Исследование направлено на оценку эффективности различных групп антибактериальных препаратов *in vitro* и *in vivo*, применяемых для лечения хронического тонзиллита в период обострения.

Материал и методы. По данным амбулаторным карт и микробиологического исследования определена группа пациентов, у которых *S. pyogenes* был основным значимым фактором развития хронического тонзиллита. Проведена оценка резистентности возбудителя диско-диффузионным методом. Изучена клиническая эффективность антибиотиков на основании

объективных критериев. Выполнено исследование изолятов *S. pyogenes*, совместно инкубированных с антибактериальным препаратом методом спектроскопии комбинационного рассеяния.

Результаты. Проведенный анализ выявил несоответствия между полученными данными диско-диффузионного метода *in vitro* и клиническими результатами. По данным диско-диффузионного теста к полусинтетическим пенициллинам были чувствительны только 87,6% пациентов, при этом в 28,2% случаев клинический эффект был неполным или отсутствовал. Незначительно, но лучшие результаты получены в случае применения ингибиторозащищенных пенициллинов. Макролиды, демонстрирующие 88,5% эффективности *in vitro*, не позволяли достигать полного эффекта от лечения у 26,6% пациентов. Сопоставимые результаты были получены при анализе цефалоспоринов. Наименьшая чувствительность *S. pyogenes in vitro* выявлена к фторхинолонам, что не позволяло достигать адекватного клинического эффекта у 28,0% пациентов. Спектроскопия комбинационного рассеяния позволила оценить чувствительность к одному из наиболее часто применяемых антибактериальных препаратов.

Выводы. Значимая разница между лабораторными и клиническими данными обусловлена не только возможной антибиотикорезистентностью, механизмы которой также рассмотрены, но и влиянием внутренних факторов, которые следует учитывать при выборе этиотропной терапии хронического тонзиллита в период обострения.

Ключевые слова: хронический тонзиллит, антибиотикорезистентность, клинический эффект, спектроскопия комбинационного рассеяния.

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INTRODUCTION

Chronic tonsillitis remains one of the prevalent chronic diseases among active population [1]. Viruses, bacteria (*Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae*) and some fungi are well known as potential causative agents maintaining the inflammatory reaction in the tonsils, combined with the action of other exogenous and endogenous adverse factors [2]. *Streptococcus pyogenes (S. pyogenes)* plays the leading role in the development of chronic tonsillitis. Being an extracellular pathogen, it persists in tonsillar tissue by expressing a broad spectrum of virulence proteins that modify immune cell response mechanisms [3].

Antibacterial drugs form the base of treatment of chronic tonsillitis. Their efficiency depends on the structure of the main substance, dosage, frequency of administration, paths and duration of administration as well as characteristics of pathogens showing susceptibility to them [4, 5]. According to the effective clinical recommendations for the diagnostics and treatment of chronic tonsillitis, upon finding the S. Pyogenes in the tonsillar tissue, the drugs of choice for the conservative treatment are the β-lactams[1]. According to study data, *S. pyogenes* retains high susceptibility to inhibitor combinations and synthetic penicillins, with resistance rates not exceeding 1%. Nevertheless, the frequency of unsatisfactory clinical outcomes remains significantly higher even with properly administered antibacterial therapy, representing a persistent challenge in clinical pharmacology that warrants comprehensive evaluation [6].

AIM

To assess both *in vitro* susceptibility of *S. pyogenes* and clinical efficacy of the most commonly used antibacterial agents for treating chronic tonsillitis (simple and grade I toxic-allergic form).

MATERIAL AND METHODS

Random sampling was used to form a group of 144 patients from three urban districts of the city of Samara, registered in follow-up care by the end of 2020 with simple and grade I toxic-allergic forms of chronic tonsillitis. The form of disease was established as per patient records according to the classification of B.S. Preobrazhensky (1954) and V.T. Palchun (1977). There were 76 male (52.8%) and 68 female (47.2%) participants of the study. According to the WHO age criteria (2016), the patients were divided into two groups: Group 1 (n= 86), young patients (age 18-44); Group 2 (n= 58), middle age patients (age 45-59). The exclusion criteria were absence of a confirmed chronic tonsillitis according to patient record data; availability of objective signs of the toxic-allergic form of grade II chronic tonsillitis (decompensated form); history of low compliance with or refusal from intercurrent therapy; history of self-treatment. The groups had statistically significant differences in the duration of the disease: in Group 1 patients, it was 7.8±2.9 years, and in Group 2 patients, 14.1±2.7 years.

In both groups, standard microbiological (culture) testing was performed of palatine tonsil exudate and posterior pharyngeal wall mucosa for aerobic and facultative anaerobic microorganisms. The evaluation of the results only considered etiologically significant pathogenic microorganisms and their diagnostically significant growth (over 104 CFU/swab or CFU/mL or CFU/g). The concomitant microflora (below 104 CFU/swab or CFU/mL or CFU/g) was disregarded. For patients with S. pyogenes identified as the primary pathogen, its antibiotic susceptibility was assessed using the Kirby-Bauer disk diffusion method *in vitro*[2]. The tested antibiotics included: semi-synthetic peniccilins, inhibitor-protected penicillins, macrolides, cephalosporins, fluoroquinolones (all commonly used to treat chronic tonsillitis). The results were interpreted using the values of measured inhibition zone diameters of

[1] Chronic tonsillitis. Clinical recommendations. 2024. URL: https://diseases.medelement.com/disease/84-2024/18329 (Last retrieved: 15.03.2025)
[2] Russian national recommendations. Identification of microorganism susceptibility to antimicrobial agents. Rev. 2024-02. Smolensk: MAKMAH, SSMU, 2024. 192 p.

microbial growth (<19 mm, antibiotic-resistant; 20-27 mm, intermediate; >28 mm, antibiotic-sensitive).

For patients with *S. pyogenes* identified as the primary pathogen, a retrospective analysis of clinical efficiency of antibacterial therapy in the acute stages was performed based on the criteria of objective assessment of the inflammatory process of the oropharyngeal cavity (V.T. Palchun, A.I. Kryukov, 2001) using historical data of patient records.

Additionally, in patients (n=113) with chronic tonsillitis, sensitivity of *S. pyogenes* to Amoxiclav was assessed by Raman scattering spectroscopy (RS). The method is well known and used successfully to test the validity of medications. Amoxiclav was chosen at the most frequently prescribed drug to treat exacerbations of chronic tonsillitis, according to the patient records, in the Cmax dosage as per prescribing label, *viz.* included 105.4 mcg/ml of amoxicillin and 28.5 mcg/ml of clavulanic acid. The spectroscopy is performed in a set of samples of oral fluid and phosphate-buffer saline as solvents with added suspension of *S. Pyogenes,* compliant with concentration of 0.5 of the McFarland standard, and, later, the antibiotic in the desired dosage. The samples were incubated in a thermostat at 37 °C for 2, 4, 6 hours, following which RS was performed. The method was implemented using a set of equipment forming a test model with a spectrometer. The analysis of spectra was performed in four zones: 1155 cm^{-1}, 1525 cm^{-1}, 1033 cm^{-1} and 1611 cm^{-1}; their final processing was done in Wolfram Mathematica 9.

Statistical methods

Statistical processing of obtained data was performed in the Statistica for Windows 7.0 software suite. The methods of descriptive statistics were used for a general characterization of the obtained data. For group mean comparisons, Student's t-test was used. Correlation analysis was performed to assess relationships between quantitative variables. The strength and direction of linear associations were determined using Pearson's correlation coefficient (for normally distributed data) or Spearman's rank correlation (for non-parametric data). Normality was evaluated with the Shapiro-Wilk test. Statistical significance was set at $p<0.05$.

RESULTS

The main pathogen of chronic tonsillitis in 113 patients of both groups was *S. pyogenes*. It was identified as the etiologically significant pathogen in 82.5% patients in Group 1 and in 72.4% patients of Group 2. In 12.8% patients of Group 1 and in 19.0% patients of Group 2, this microorganism was plated with other significant pathogens, e.g. *Streptococcus pneumoniae* and/or *Staphylococcus aureus*. At the same time, in Group 2 in a credibly larger number of cases (Group 1: 19.0% vs. Group 2: 4.7%, $p<0.001$) presence of *Candida spp.* was identified.

According to patient record data, treatment of exacerbations of chronic tonsillitis of the simple and grade I toxic-allergic forms mediated by *S. pyogenes*, various antibiotics were used. Most frequently, the following were prescribed: inhibitor-protected penicillins, macrolides, cephalosporins, semi-synthetic penicillins, in some cases, fluoroquinolones. The analysis of clinical efficiency of the use of those groups of antibacterial agents in the treatment of exacerbations showed various results (**Fig. 1**).

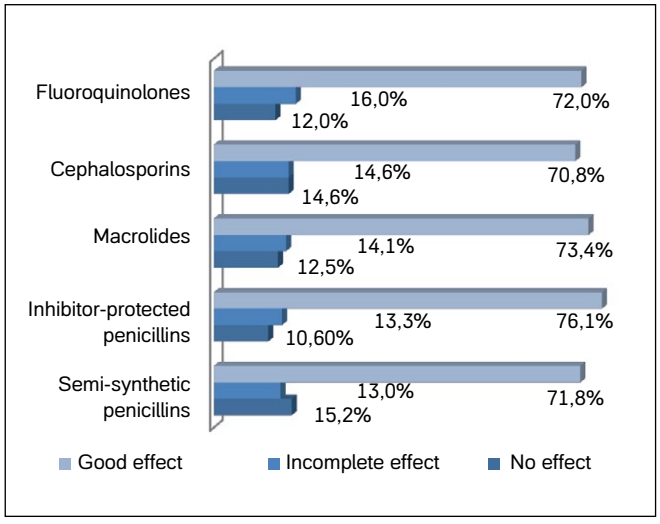

Figure 1. *Clinical efficacy of antibacterial agents in the treatment of exacerbations of chronic tonsillitis (simple and toxic-allergic grade I forms) in patients.*

Рисунок 1. *Показатели клинической эффективности терапии обострений хронического тонзиллита простой и токсико-аллергической I степени форм различными видами антибактериальных препаратов у пациентов.*

Regardless of the type of the antibacterial drug, 78 (69.0%) patients did not reach a positive clinical effect or it was incomplete and required adjustment of the scheme of therapy (increase of course duration, change of average daily dose, replacement or addition of a second antibacterial drug). Among the patients in whom a good clinical effect was reached in the treatment of exacerbation, no statistically significant variations were identified that would relate to the selection of a specific antibacterial drug.

The results of the disk-diffusion method of assessment of sensitivity of *S. pyogenes* to various types of antibacterial drugs *in vitro* did not identify a single completely resistant strain. At the same time, data was obtained indicating intermediate values of measured inhibition zone diameters of microbial growth of *S. pyogenes*, which was likely mediated by the active process of formation of antibiotic resistance (**Fig. 2**).

The results of the correlation analysis showed the presence of a moderate positive connection ($r=0.607$) between the results of the intermediate sensitivity *in vitro* and the data on incomplete or lacking clinical effect *in vivo* (**Fig. 3**).

The RS data showed that in the cases of sensitivity of *S. pyogenes* to Amoxiclav in the predominant number of samples, within the first two hours of incubation disappearance of linear values characterizing the lysis of the etiological pathogen is found. At the same time, in some patients, disappearance if linear values was identified only after six hours of incubation.

DISCUSSION

Chronic tonsillitis, particularly its toxic-allergic forms, remains a challenging clinical condition, largely due to the growing problem of antibiotic resistance. The results of this study provide direct confirmation of this hypothesis.

Semi-synthetic penicillins (amoxicillin and ampicillin) are traditionally prescribed in exacerbations of chronic tonsillitis due to their affordable price and good bioavailability. However, as the disk-diffusion test showed, in 12.4%

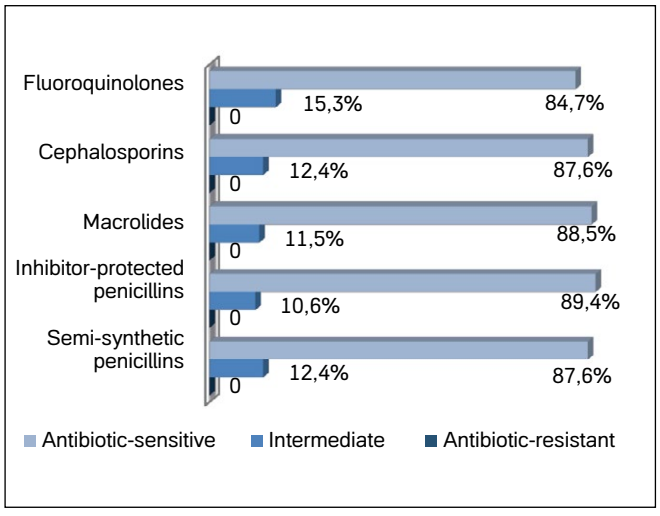

Figure 2. *Susceptibility of S. pyogenes to various antibacterial agents in patients with chronic tonsillitis (simple and toxic-allergic grade I forms) in vitro.*

Рисунок 2. *Показатели чувствительности S. pyogenes к различным видам антибактериальных препаратов у пациентов с хроническим тонзиллитом простой и токсико-аллергической I степени форм in vitro.*

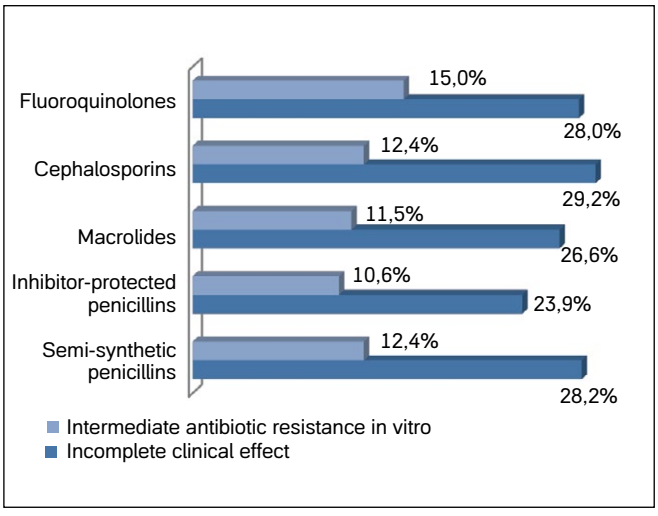

Figure 3. *Comparative analysis of intermediate inhibition zones for S. pyogenes in vitro and absent or incomplete clinical effects of antibacterial agents in the treatment of chronic tonsillitis exacerbations (simple and toxic-allergic grade I forms) in patients.*

Рисунок 3. *Сравнительные данные между показателями промежуточных зон подавления роста S. pyogenes in vitro и отсутствующим или неполным клиническим эффектом от применения различных видов антибактериальных препаратов при лечении обострений хронического тонзиллита простой и токсико-аллергической I степени форм у пациентов.*

patients, intermediate values of inhibition of bacterial growth of *S. pyogenes* were found, which indicates formation of resistance. The phenomenon may be explained by the necessity of performing a lengthy course of therapy with semi-synthetic penicillins with possible dosage adjustment and resulting low compliance of patients with the therapy regime. As little as 8% of patients are capable of keeping this regime [7]. Besides, bacterial internalization into mucosal epithelial cells renders them inaccessible to β-lactams [8]. Despite rare *in vitro* penicillin resistance (less than 5%), clinical treatment failure is typically attributed to biological and behavioral factors [9].

Transition to penicillins combined with inhibitors such as amoxicillin or clavulanic acid provided improved results of treatment of patients with chronic tonsillitis. Their clinical inefficiency, according to the results of the study, was 10.6%, which is slightly lower than that of semi-synthetic analogues. Clavulanic acid inhibits most β-lactamases, however, it is not efficient against strains with modified penicillin-binding proteins [10]. This correlates with the data of another study, in which the reasons of resistance included modification of targets or hyper-production of enzymes. In order to prevent the activation of such a mechanism of resistance, prescription of such inhibitor-protected penicillins require strict supervision [11].

Paradoxical results were seen in the analysis of macrolides. With the sensitivity of 88.5% *in vitro*, their clinical efficiency was only 73.4%. These results may be explained by several factors. First, since 2007 the intake of macrolides in Russia grew by 50%, which directly correlates with the spreading of resistance via studied mechanisms of erm-mediated modification of targets [12]. Second, the cross-resistance within a class lowers the efficiency of all macrolides, even if *in vitro* sensitivity remains high [13]. It is to be noted that in outpatient practice, this group of antibacterial agents is prescribed for their convenience (a short period of intake with a modest number of side effects).

Cephalosporins showed a level of inefficiency comparable with inhibitor-protected penicillins (14.6%). The limit to their use is related with the prevalence of strains producing extended spectrum β-lactamases (ESBL) [14]. At the same time, cephalosporins of third generation remain medications of choice in exacerbated infections since they retain their activity against most strains of streptococci.

Fluoroquinolones, despite their low clinical efficiency, demonstrate the intermediate area of growth inhibition for 15.3% strains. Their limited efficiency against *S. pyogenes* is related to the fact that fluoroquinolones are more active against gram-negative bacteria, whereas gram-positive bacteria develop resistance via mutation in the gyrA/parC genes and activation of efflux pumps. This renders their use in chronic tonsillitis less justified, especially in the regions with high levels of intake of fluoroquinolones [15].

CONCLUSION

Thus, the sensitivity analysis of pathogens isolated from chronic tonsillitis patients revealed no strains of *S. pyogenes* fully resistant to the antibiotics used for this condition. The obtained values of sensitivity of *S. pyogenes in vitro* are higher than the values of clinical efficiency in vivo for the group of semi-synthetic penicillins by 18.0%; inhibitor-protected penicillins, by 14.9%; cephalosporins, by 19.2%; fluoroquinolones, by 15.0%; macrolides, by 17.1%, respectively. Currently, inhibitor-protected penicillins and cephalosporines may remain first-line medications for the therapy of chronic tonsillitis, while the use of macrolides and fluoroquinolones in the cases of streptococcus infections should be restricted reserving them for cases of confirmed sensitivity. Raman spectroscopy proved to be an effective rapid method for personalized susceptibility testing and may find wide application in clinical practice.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical Approval Statement. The study was conducted at the Department of Pharmacy in 2024. A positive conclusion was received from the LEC of the Reaviz Medical University No. 08 dated 23.05.2024.	***Этическая экспертиза.*** Исследование проведено на базе кафедры фармации в 2024 году. Получено положительное заключение ЛЭК Медицинского университета «Реавиз» от 23.05.2024 г. №08.
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Zolotarev P.N.: concept and design of the study, editing of the manuscript. Burenkov E.S.: data collection and processing, writing of the original text. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Золотарев П.Н. – концепция и дизайн исследования, редактирование рукописи. Буренков Е.С. – сбор и обработка данных, написание оригинального текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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