

## ANTIBIOTIC THERAPY IN THE COMPLEX PATHOGENIC TREATMENT OF PATIENTS WITH SIALOLITHIASIS IN THE STAGE OF EXACERBATION OF CHRONIC SIALOADENITIS

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### Abstract

The issue of complex treatment of patients with chronic sialoadenitis and sialolithiasis in the stage of exacerbation and in the presence of purulent exudate remains relevant to this day. The purpose of this study was to evaluate the antimicrobial efficacy of the combination of amoxicillin + cloxacillin + *Lactobacillus sporogenes* (ACL) complex in patients with chronic sialoadenitis and sialolithiasis in the stage of exacerbation of the disease and in the presence of purulent exudate.

Two groups of patients, depending on the antibiotic therapy received with signs of purulent exudation from the excretory ducts of the affected glands. Diagnoses were established on the basis of clinical, laboratory (clinical blood assay; type II immunological blood test, immunoenzymatic assessment of blood serum to detect specific antibodies of the secondary immune response to mumps and cytomegaly viruses), sialosonographic and X-ray studies. The effectiveness of ACL complex effectiveness was evaluated using clinical and microbiological methods, as well as in comparison with the clinical effectiveness of erythromycin.

The data of microbiological and clinical studies carried out after treatment with ACL complex indicate that it effectively acts in the presence of purulent inflammation in the large salivary glands and restores the natural ratio of microorganisms in the excretory ducts of the affected salivary glands. In addition, the results of a clinical study made it possible to note that ACL did not cause side effects and allergic reactions and can be used in patients with immunopathological conditions secondary to persistent viral infection.

**Keywords:** amoxicillin, cloxacillin, *Lactobacillus sporogenes*, chronic sialoadenitis

## Introduction

The issue of complex treatment of patients with chronic sialoadenitis and sialolithiasis in the stage of exacerbation and in the presence of purulent exudate remains relevant to this day [1]. However, the lack of consensus on the etiology and pathogenesis of these diseases leads to a decrease in the effectiveness of treatment of this contingent of patients [2, 3]. The most optimal and highly effective methods are those with etiotropic and pathogenic direction with important adequate diagnostic measure [4, 5]. In the light of modern ideas about the etiology of chronic inflammation in the salivary glands, induced by the persistence of mumps and cytomegalovirus viruses, with the subsequent development of immunopathology, it is necessary to revise the approaches to the treatment of these patients in the presence of a microbial infection exacerbating the course of the disease [6]. In such cases, antibiotic therapy retains its importance [7]. When choosing an antibiotic, it is necessary to take into account not only the sensitivity of microorganisms to the agent and its tropism to certain tissues, but also the possibility of an unwanted immunosuppressive effect [8, 9] on the patient's pathologically altered immune homeostasis [10, 11]. Antimicrobial agents in the complex treatment of patients with chronic sialoadenitis in the acute stage can include only antibiotics with a minimal immunosuppressive effect [12]. In this regard, our attention was attracted by the combination of amoxicillin + cloxacillin + *Lactobacillus sporogenes* (ACL), which in its antibacterial and pharmacokinetic properties surpasses traditional complex antibacterial agents and, due to the presence of lactobacilli *Lactobacillus sporogenes* in its contents, has the immunomodulatory properties [14, 15]. ACL is a complex that combines the properties of both an antibiotic and a probiotic. The complex includes: amoxicillin – an antibiotic from the group of semisynthetic aminopenicillins [16]; cloxacillin – a new antibiotic from the group of semi-synthetic penicillinase-stable penicillins [17] and lactobacillus *Lactobacillus sporogenes* – a probiotic agent. The combination of amoxicillin and cloxacillin has a wider spectrum of antibacterial action compared to other drugs in this class [17]. The presence in the

complex of lactobacilli *Lactobacillus sporogenes* helps to avoid dysbiosis and dysbacteriosis associated with the use of antibiotics, and provides the immunomodulatory properties of ACL. ACL can be recommended for use in the treatment of polymicrobial, mixed infections of ENT organs, lower respiratory tract, some intestinal infections, skin and soft tissues, bones and joints, endocarditis; in dental interventions [18]. We have not found data on the use of such a complex in the treatment of diseases of the salivary glands. However, the similarity of the microbial landscape of the oropharynx with the microbial landscape of the excretory ducts of the large salivary glands allowed us to conduct studies to determine the effectiveness of this drug in the treatment of patients with sialolithiasis with exacerbation of chronic inflammation and purulent exudation.

The **purpose** of this study was to evaluate the antimicrobial efficacy of the ACL complex in patients with chronic sialoadenitis and sialolithiasis in the stage of exacerbation of the disease and in the presence of purulent exudate.

## Methods

To clarify the expediency of ACL complex administration, we formed two groups of patients, depending on the antibiotic therapy received. Control group 1 included 20 patients with chronic sialoadenitis and sialolithiasis of the submandibular salivary glands. The main group 2 consisted of 23 patients with chronic inflammatory diseases of the salivary glands with sialolithiasis, 20 of whom suffered from chronic sialoadenitis and sialolithiasis of the submandibular salivary glands, 3 patients with chronic sialoadenitis and sialolithiasis of the parotid glands. All patients of both groups had signs of purulent exudation from the excretory ducts of the affected glands. Diagnoses were established on the basis of clinical, laboratory (clinical blood assay; type II immunological blood test, immunoenzymatic assessment of blood serum to detect specific antibodies of the secondary immune response to mumps and cytomegaly viruses), sialosonographic and X-ray studies.

We studied the qualitative and quantitative composition of microflora of the main excretory ducts of the affected salivary glands in patients of

the main group before treatment and on the seventh day of therapy. Microbiological studies were carried out according to generally accepted methods in the conditions of the microbiological laboratory of the Department of Clinical Microbiology and Immunology of Kharkiv Medical Academy of Postgraduate Education. The material was collected using a cannula needle and a sterile disposable syringe after antiseptic treatment of the oral cavity with furacilin solution (1: 5000) and the orifices of the excretory ducts with 1% iodine solution. All patients of both groups received complex treatment, which consisted of minimally invasive surgical interventions on the excretory ducts of the affected glands in order to remove calculus and reparative formation of a new duct opening to restore the secretory function of the gland according to a known technique. Also, the patients underwent etiotropic and pathogenically directed drug infusion-detoxification, anti-inflammatory, vitamin and pulse therapy. ACL (amoxicillin - 250.0 mg, cloxacillin sodium - 250.0 mg, Lactobacillus Sporogenes - 6000000 Spg) agent was used as antibiotic therapy in the main group in the dosage of 1 capsule 3 times a day for 7 days, and in the control group, erythromycin (an antibiotic from the macrolide group, tropic to the tissues of the salivary glands), 2 tablets (0.2 g) 4 times a day, also for 7 days. The effectiveness of ACL complex effectiveness was evaluated using clinical and microbiological methods, as well as in comparison with the clinical effectiveness of erythromycin.

## Results

Data on the results of a qualitative and quantitative microbiological study of the secretion of the excretory ducts of the salivary glands in patients of the main group on the 1st and 7th days of treatment are presented in Table 1.

The data obtained were compared with the known literature data on the microbial landscape vegetating in the oropharynx of healthy people. Each type of opportunistic microorganisms is known to have a maximum permissible number of microbial bodies per 1 gram of biopsy, the so-called "critical number". Based on the literature data, the critical number is individual for each type of microorganism. The results obtained indicated that

after the complex treatment, including antibiotic therapy with the ACL complex, the spectrum of microflora decreased and approached that characteristic of healthy people. The number of streptococci, staphylococci and peptostreptococci was found to be below the critical number. The number of Neisseria and pneumococci was close to the number typical for healthy people.

During clinical examination, patients of both groups suffering from sialolithiasis of the submandibular glands with exacerbation of chronic sialoadenitis on admission presented with painful swelling under the mandible, pain under the tongue along its excretory duct. Clinical examination showed a sharply enlarged, dense painful salivary gland. In 41 patients (95%), there was an enlargement in other large salivary glands. At the same time, they were painless, doughy, their salivary function remained normal. Examination of the oral cavity detected hyperemia and edema of the mucous membrane of the floor of the mouth. The orifice of the duct in all patients was spasmodic; gentle massaging of the gland was used to obtain purulent discharge from the duct. Palpation along the duct determined the presence of calculus. In chronic sialoadenitis with sialolithiasis of the parotid glands, patients presented with a sharply painful swelling of the parotid region and an unpleasant taste in the mouth. Examination revealed a sharply enlarged, dense, painful parotid gland with clear contours. In the oral cavity in the area of the mouth of the excretory duct, Mursson's sign was detected, the orifice was gaping, and when massaged, the gland released a scanty purulent discharge from the duct.

On the 7th day of complex therapy and removal of sutures in the oral cavity, history were thoroughly taken from patients of the main groups, a clinical examination was carried out, and samples were also taken from the excretory ducts of patients of the main group for repeated microbiological examination. Data on the nature of patient presentation and clinical manifestations of treatment are presented in Table 2.

As evidenced by the data presented in Table 2, the effectiveness of eliminating signs of inflammation in the gland and in the postoperative

wound in the area of the excretory duct of the gland in the course of complex treatment with the antibiotic ACL is higher than in the group with the use of erythromycin. Manifestations of allergic reactions were practically not observed in the main group, whereas in the control group these manifestations reached 20-25%.

### Discussion

In the literature, there are experimental data aimed at the treatment of inflammatory processes in the oral cavity, depending on the etiological factor [19, 20]. At the same time, the etiological aspects of the occurrence of calculous sialoadenitis in the literature are presented extremely controversially. The existing data indicate many causal factors, among which the inflammatory theory [21] and the theory of mineralization disorders prevail, as well as the state of the environment [22, 23], microbial factor, vitamin deficiency, hormonal and nervous regulation disorders [24, 25].

Previously published data on the study of the morphological pathogenesis of stone formation are more definite. Pathological changes have, as a rule, the same type of picture, consisting in varying degrees, expressed lymphocytic infiltration, fibrosis and sclerosis [21]. Moreover, a number of factors can be synergistic in development. Thus, previously obtained data on the role of tobacco smoking in stone formation [26] force us to pay more attention to the state of the oral cavity in smokers [27] and pathological processes in the oral cavity [28].

Modern studies also indicate the presence of calcium and phosphorus microlites, as well as amylase crystals in the large salivary glands in sialolithiasis, the formation of which is interpreted as a consequence of the proliferative or destructive direction of the inflammatory process especial with antibiotic resistance [29]. Providing such a focus of chronic inflammation is closely related to disorders of immune homeostasis of various etiologies [30].

However, the key in the introduction of patients with sialolithiasis is the presence of purulent complications, which forces the use of antibiotics for the management of such patients. We got high effectiveness of eliminating signs of inflammation in the gland and in the postoperative wound in the

area of the excretory duct of the gland in the course of complex treatment with the complex ACL is higher than in the group with the use of erythromycin.

Another important factor was the small manifestations of allergic reactions were practically not observed in the main group, whereas in the control group these manifestations reached 20-25%.

**Conclusions:** The data of microbiological and clinical studies carried out after treatment with the amoxicillin + cloxacillin + *Lactobacillus sporogenes* complex indicate that it effectively acts in the presence of purulent inflammation in the large salivary glands and restores the natural ratio of microorganisms in the excretory ducts of the affected salivary glands.

In addition, the results of a clinical study made it possible to note that ACL did not cause side effects and allergic reactions and can be used in patients with immunopathological conditions secondary to persistent viral infection.

The above allows us to recommend the use of amoxicillin + cloxacillin + *Lactobacillus sporogenes* complex in the complex treatment of patients with various chronic inflammatory diseases of the salivary glands during exacerbations and the presence of purulent exudation in them.

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### References

1. Araújo RV, Milani BA, Martins IS, Vilela Dias EM, Bernalda-Paredes WE. An Extraoral Surgical Approach to Treat Chronic Submandibular Sialolithiasis - A Case Series. *Ann Maxillofac Surg.* 2020;10(2):537-542. doi:10.4103/ams.ams\_102\_20
2. Schapher M, Koch M, Weidner D, et al. Neutrophil Extracellular Traps Promote the Development and Growth of Human Salivary Stones. *Cells.* 2020;9(9):2139. Published 2020 Sep 22. doi:10.3390/cells9092139

3. Polyvianna Y., Chumachenko D., Chumachenko T. Computer aided system of time series analysis methods for forecasting the epidemics outbreaks. 2019 15th International Conference on the Experience of Designing and Application of CAD Systems, CADSM 2019:1-4. doi: 10.1109/CADSM.2019.8779344
4. Kraaij S, Brand HS, van der Meij EH, de Visscher JG. Relationship between volume of submandibular salivary stones in vivo determined with Cone-Beam Computer Tomography and in vitro with micro-Computer Tomography. *Med Oral Patol Oral Cir Bucal*. 2021;26(5):e598-e601. Published 2021 Sep 1. doi:10.4317/medoral.24605
5. Gargin V., Muryzina I., Shcherbina N., Nechyporenko A., Baryshevska V., Vorobyova O., Alekseeva V. Relationship between bone density of paranasal sinuses and adrenal steroids pattern in women during menopausal transition. *Anthropological Review*. 2020;83(4):407–418. doi: 10.2478/anre-2020-0031
6. Nebogatov SS, Chulak LD, Shuturminsky VG, Chulak OL, Tatarina OV, Badiuk NS. Dental aesthetic inlay core – practical evaluation. *Pharmacologyonline* 2021;2:742-752.
7. Salama AH. Antimicrobial peptides synthesis and mechanism of action. *Pharmacologyonline* 2021;2:1404-1410.
8. Pelchen-Matthews A., Ryom L., Borges Á.H., et al. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. *AIDS*. 2018;32(16):2405-2416. doi:10.1097/QAD.0000000000001967
9. Shepherd L, Borges Á, Ledergerber B, et al. Infection-related and -unrelated malignancies, HIV and the aging population. *HIV Med*. 2016;17(8):590-600. doi:10.1111/hiv.12359
10. Avilova O, Shyian D, Marakushin D, Erokhina V, Gargin V. Ultrastructural changes in the organs of the immune system under the influence of xenobiotics. *Georgian Med News*. 2018;(279):132-137.
11. Bondarenko AV, Pokhil SI, Lytvynenko MV, Bocharova TV, Gargin VV. Anaplasmosis: experimental immunodeficient state model. *Wiad Lek*. 2019;72(9 cz 2):1761-1764.
12. Ivannik VYu, Torianyk II, Moiseienko TM, et al. Antimicrobial Activity Derivatives 2Hpirano[2,3-c]pyridines against Pathogens of Intestinal Yersiniosis. *J Pharm Nutr Sci* 2021; 11: 87-92.
13. Sayer B, Bortone B, Sharland M, Hsia Y. Fixed-dose combination antibiotics: The search for evidence using the example of ampicillin-cloxacillin. *Br J Clin Pharmacol*. 2021;87(7):2996-2999. doi:10.1111/bcp.14711
14. Falade OB, Falusi AG, Olaniyi AA, Ezeasor C, Kwasi DA, Babalola CP. Significant Pharmacokinetic Interactions Between Quinine and Ampicillin-Cloxacillin Combination. *Drugs R D*. 2016;16(2):193-203. doi:10.1007/s40268-016-0128-x
15. Nazaryan RS, Kryvenko LS, Gargin VV. The role of nitric oxide synthase in the modulation of the immune response in atopic disease. *New Armenian Med J* 2017;11(2):52-57.
16. Gurusamy KS, Koti R, Toon CD, Wilson P, Davidson BR. Antibiotic therapy for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in non surgical wounds. *Cochrane Database Syst Rev*. 2013;(11):CD010427. doi:10.1002/14651858.CD010427.pub2
17. Al-Ahmad A, Elamin F, Gärtner R, et al. New Bacterial Combinations in Secondary Endodontic Infections of Patients with a Recent Systematic Antibiotic Therapy. *Monogr Oral Sci*. 2021;29:144-154. doi:10.1159/000510190
18. Nechyporenko AS, Alekseeva VV, Sychova LV, Cheverda VM, Yurevych NO, Gargin VV. Anatomical prerequisites for the development of rhinosinusitis. *Lek Obz* 2020;6(10):334-338.
19. Kovach I, Kravchenko L, Khotimska Y, Nazaryan R, Gargin V. Influence of ozone therapy on oral tissue in modeling of chronic recurrent aphthous stomatitis. *Georgian Med News*. 2017;(264):115-119.

20. Fesenko D, Glazunov O, Nakonechna O, Nazaryan R, Gargin V. Consequences of microsequences of microcirculatory disturbances of oral mucosa in modeling of rheumatoid arthritis. *Georgian Med News*. 2019;(295):137-140.
21. Pachisia S, Mandal G, Sahu S, Ghosh S. Submandibular sialolithiasis: A series of three case reports with review of literature. *Clin Pract*. 2019;9(1):1119. Published 2019 Mar 20. doi:10.4081/cp.2019.1119
22. Ludwicki J.K., Góralczyk K., Struciński P., et al. Hazard quotient profiles used as a risk assessment tool for PFOS and PFOA serum levels in three distinctive European populations. *Environ Int*. 2015;74:112-118. doi:10.1016/j.envint.2014.10.001
23. Lenters V, Thomsen C, Smit LA, et al. Serum concentrations of polybrominated diphenyl ethers (PBDEs) and a polybrominated biphenyl (PBB) in men from Greenland, Poland and Ukraine. *Environ Int*. 2013;61:8-16. doi:10.1016/j.envint.2013.09.001
24. de Almeida AS, Kato CNO, Jácome-Santos H, Pinheiro JJ, Mesquita RA, Abreu LG. A retrospective analysis of oral and maxillofacial lesions in children and adolescents reported in two different services. *J Clin Exp Dent*. 2021;13(9):e894-e905. Published 2021 Sep 1. doi:10.4317/jced.58231
25. Denga O, Pyndus T, Gargin V, Schneider S. Influence of metabolic syndrome on condition of microcirculatory bed of oral cavity. *Georgian Med News*. 2017;(273):99-104.
26. Jin YJ, Han YE, Choi HG. The association between sialolithiasis and smoking, alcohol drinking and obesity in Korea: a nested case-control study. *BMC Public Health*. 2020;20(1):516. Published 2020 Apr 17. doi:10.1186/s12889-020-08674-w
27. Nazaryan R, Kryvenko L, Zakut Y, Kamaukh O, Gargin V. Application of estimated oral health indices in adolescents with tobacco addiction. *Pol Merkur Lekarski*. 2020;48(287):327-330.
28. Popova TM, Kryvenko LS, Tishchenko OV, Nakonechna OA, Podrigalo LV, Nessonova TD, Gargin VV. Effect of Electronic Cigarettes on Oral Microbial Flora. *J Pharm Nutr Sci* 2021; 11(1):54-64
29. Kon K, Rai M. Antibiotic Resistance: Mechanisms and New Antimicrobial Approaches. *Antibiotic Resistance: Mechanisms and New Antimicrobial Approaches*; 2016. p. 1-413.
30. Krivenko S, Lukin V, Krylova O, Kryvenko L, Egiazarian K. A fast method of visually lossless compression of dental images. *Appl Sci* 2021;11(1):1-14.

**Table 1.** The results of a microbiological study of the secretion of the excretory ducts of the large salivary glands in patients suffering from sialolithiasis with exacerbation of chronic sialoadenitis before and after treatment

Microorganism type	Critical number	Microorganism number		
		In healthy subjects	In patients before treatment	In patients after treatment
Streptococci	$10^6-10^7$	$3 \cdot 10^5$	$1 \cdot 10^6$	$1 \cdot 10^5$
Pneumococci	$10^6-10^7$	$2 \cdot 10^6$	$1 \cdot 10^4$	$1 \cdot 10^6$
Stomatococci	$10^6-10^7$	$1 \cdot 10^5$	$2 \cdot 10^6$	$1 \cdot 10^5$
Staphylococci	$10^4-10^5$	$1 \cdot 10^4$	$1 \cdot 10^4$	-
Neisseria	$10^6-10^7$	$1 \cdot 10^7$	$1 \cdot 10^6$	$5 \cdot 10^6$
Peptostreptococci	$10^2-10^3$	-	$1 \cdot 10^2$	$1 \cdot 10^1$

**Table 2.** The nature of presentation and clinical manifestations in patients with sialolithiasis with exacerbation of chronic sialoadenitis after treatment

Presentation and clinical manifestations	Main group (23 patients)	Control group (20 patients)
1. Presentation:		
a) tenderness in the area of the gland:		
- non-tender	22 (95.9 %)	18 (90%)
- tender	1 (4.1%)	2 (10 %)
- painful	-	-
b) tenderness in the area of postoperative wound:		
- non-tender		
- painful	23 (100 %)	18 (80 %)
c) general impairment:		
- itching, redness of the skin	-	2 (10 %)
- diarrhea	-	4 (20 %)
- nausea, vomiting	1 (4,1%)	5 (25 %)
- stomachache	-	-
		4 (20 %)

2. Clinical manifestations:		
a) degree of gland enlargement:		
- not enlarged	18 (79.5 %)	14 (70 %)
- slightly enlarged	5 (20.5 %)	6 (30 %)
- enlarged	-	-
b) gland consistency:		
- soft elastic	21 (91.8 %)	16 (80 %)
- dense elastic	2 (8.2 %)	4 (20 %)
- dense	-	-
c) signs of inflammation in the area of the postoperative wound (hyperemia, edema):		
- none	23 (100 %)	17 (85 %)
- moderate	-	3 (15 %)
- severe	-	-
d) saliva discharge from the duct:		
- in sufficient quantity	17 (75.4 %)	14 (70 %)
- in moderate quantity	6 (24.6 %)	6 (30 %)
- single discharge	-	-
e) saliva condition:		
- liquid, transparent	22 (95.9 %)	17 (85 %)
- thick, viscous	1 (4.1 %)	3 (15 %)
- dough-like with an admixture of pus	-	-
f) manifestations of side-effects of antibiotics:		
- itching, hyperemia, local hyperemia, skin eruption	-	4 (20 %)
- yellow coating of the tongue	-	5 (25 %)
- dryness, redness of the oral mucosa	-	5 (25 %)