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Practical application of modern methods of inpatient streptococcal infection diagnostics

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It is commonly known that acute tonsillites are in most cases caused by viral infections. Only ca. 20% of patients require antibacterial therapy, including cases of the group-A-β-hemolytic-streptococcus-caused tonsillites. Etiologic diagnostics of acute tonsillitis is extremely complicated in terms of both clinical symptoms and bacterial inflammation marker levels, which is why it is positive result of a cultural study of palatine tonsillar materials that should serve as an indication to prescription of systemic antibacterial therapy. Express test for detection of the group A β-hemolytic streptococcus, comparable to the cultural study method in terms of sensitivity and specificity, helps reasonable approach to the treatment of acute tonsillites.
Keywords: *acute tonsillitis, express test, group A β-hemolytic streptococcus, antibiotics.*

It is common knowledge that acute tonsillitis syndrome in children with fever and deposits on palatine tonsils is in most cases of viral etiology and does not required systemic antibacterial therapy. However, ca. 20% of tonsillites are caused by a serious bacterial causative agent – group A β-hemolytic streptococcus (GABHS) [1]. Undiagnosed and untreated streptococcal tonsillitis is fraught with severe purulent (pharyngeal abscesses of different localization, purulent lymphadenites) and systemic (acute rheumatic fever, post-streptococcal reactive arthritis, streptococcal toxic shock syndrome, PANDAS syndrome, acute post-streptococcal glomerulonephritis) complications. Eradication of streptococcus after systemic antibacterial therapy allows preventing such complications.

It is common knowledge that it is almost impossible to differentiate between viral and streptococcal tonsillites on the basis of clinical symptoms. Only catarrhal phenomena may indicate a respiratory viral infection with tonsillites with high probability, while hepatosplenomegaly rules out infectious mononucleosis. That is why it is almost impossible to decide at the primary examination of the patient whether systemic antibacterial treatment is justified. It has also been proved that increase in the level of bacterial inflammation markers (leukocytes, C-reactive protein, procalcitonin) does not imply bacterial etiology of acute tonsillitis [2, 3]. Only bacteriological analysis of the material from palatine tonsils and posterior pharyngeal wall allows confirming or ruling out a bacterial infection and, therefore, determining need in or groundlessness of antibacterial therapy prescription.

Unfortunately, in practice, bacteriological analysis for etiologic diagnostics of acute tonsillites is conducted impermissibly rarely. It is easier for doctors to prescribe an antibiotic at once, at the primary examination, even if there are no indications to treatment, than to call paramedical personnel to sample material for examination. Moreover, in the vast majority of cases doctors cannot learn preliminary laboratory culture results despite the fact that *Streptococcus pyogenes* starts growing in the first day; in practice, doctors receive bacteriological analysis results after 5-7 days at best, which, without any doubt, is inadmissible in case of an acute disease. Moreover, not all medical establishments have a microbiological laboratory; this results in an even more complicated procedure of analysis.

Clinicians have also shaped a stereotype that deposits on palatine tonsils are pus and that their presence is an indication to antibiotic prescription at best; and an indication to mechanical

removal of tonsillar deposits, which in practice is extremely dangerous and contraindicated in case of an acute disease, at worst. This practice is partly caused by the use of the outdated classification of anginas suggested by a prominent otolaryngologist I.B Soldatov, who distinguished between catarrhal, follicular, lacunar and necrotic types of angina; this indirectly influences the way doctors see etiology of tonsillitis. Nowadays, we are to use the International Classification of Diseases (10^{th} revision), which distinguishes between streptococcal and non-streptococcal acute tonsillites and pharyngites on a rational basis. That is why doctors ought to clarify etiology of the disease in order to establish diagnosis.

According to the statistics, cultural studies are conducted extremely rarely [4, 5]. As a rule, they are carried out as per the following scenario. Deposits on palatine tonsils of a feverish child give doctors grounds for prescribing antibacterial therapy. A nurse samples material for analysis the next day. As in a vast majority of cases patients recover by the time bacteriological study results are obtained, it does not matter whether streptococcus was present or not. Moreover, results of the study are almost always negative: firstly, in most cases acute tonsillites are viral, which is why it is not possible to detect streptococcus on tonsils before prescription of antibiotic as well; secondly, if tonsillitis is of streptococcal nature, one dose of antibiotic is usually sufficient to obtain a negative result of the microbiological study due to high sensitivity of streptococcus to most antimicrobial drugs.

Given difficulties of conducting cultural studies and their high cost, express tests for detection of the GABHS have become popular. The most convenient to use are express tests of the II generation; their mechanism of action is based on the extraction of the group-specific carbohydrate group A streptococcal antigen out of streptococci in the sample. Apart from latex agglutination, there are other modern technologies identifying the group A streptococcus-specific RNA sequence. At present, sensitivity of express tests has achieved 95%, specificity – almost 100% [6]. The main advantage of express diagnostics tests is the rapidity of results' generation. Their compactness and ease of use allow revealing etiology of tonsillitis during the visit to a doctor or at the patient's bedside; this is advantageous not only for patients, who obtain correct diagnosis and prescription of reasonable antibacterial or symptomatic therapy within a few minutes, but also for a doctor's image. At present, express diagnostics results are so accurate that a control bacteriological study is unnecessary.

In 2006-2009, scientific research aimed at determination of optimal diagnostic criteria and the subsequent etiotropic treatment of acute tonsillitis and development of the corresponding algorithm, which would allow avoiding prescription of antimicrobial therapy in children under 3 years of age and in older children with catarrhal phenomena prior to the results of GABHS analysis, at the diagnostics and medical rehabilitation department (DMRD) at the SCCH. In case an antibiotic had been prescribed without any analysis, it was necessary to evaluate its efficacy within 48 hours (relief of fever); if the temperature remained at the same level, it was allowed to cancel antibacterial therapy [7]. Subsequently, such management algorithms for children with acute tonsillitis were recommended by the Practice guidelines for the diagnosis and management of GABHS-pharyngitis of the Infectious Diseases Society of America (IDSA, 2012) [8], National guidelines for the treatment of acute pharyngites in children of the Italian National Institute of Health (2012) [9] etc. The use of this algorithm in daily practice of the department allowed reducing the rate of antibacterial therapy prescription at viral tonsillites by 2013. Only 10% of the department's patients with previously prescribed antibacterial therapy continued receiving it (down from 21%), while the number of children with viral tonsillitis who had not initially been receiving antibiotics increased from 30 to 53%. Hospital prescription of an antibiotic to the children who had not been receiving domiciliary reduced from 20 to 3%. Antimicrobial treatment was delivered to children with concurrent bacterial infection (e.g., in case of development of acute otitis media in the setting of acute respiratory viral infection) and when acute tonsillitis was accompanied by significant increase in bacterial inflammation markers (CRP >60 mg/l, PCT – 2 ng/ml).

Express tests for diagnostics of acute streptococcal tonsillites have been used at the SCCH since 2008; "sandwich" immunoassay Streptatest (Dectra Pharm, France) has been used as a method of express diagnostics since 2010. It requires 6 minutes at the most. The test's sensitivity is 96.8%, specificity – 94.7%, positive predictive value – 98.9%, negative predictive value – 98.9%. According to the study of 525 patients, total correlation with cultural bacteriological method is 95.2% (p=0.95) [10].
204 children with diagnosis "Acute tonsillitis" were examined at the SCCH DMRD in the given period; material of palatine tonsils and posterior wall of pharynx was sampled for express tests in all children. We received 25 positive and 179 negative results. We also conducted cultural analysis of the material in 122 cases. We revealed only 1 discrepancy: express test was positive, cultural analysis – negative; most probably, due to the mistake made during material sampling for bacteriological analysis. Thus, we may state that Streptatest has high level of sensitivity and specificity comparable to such level of the cultural study.
Low cost of this method allows implementing it into diagnostics not only at major establishments, but also at smaller clinics without a laboratory and its application by private practice doctors. Moreover, the possibility to conduct express diagnostics at the patient's bedside, which allows avoiding unreasonable hospitalization of the patient and unreasonable prescription of antibiotics at viral tonsillites, has great pharmacoeconomic advantages.
At the moment, the use of Streptatest is a routine procedure for etiologic diagnostics of acute tonsillites by pediatricians, infectologists and otolaryngologists at the SCCH.

Several clinical cases of practice of the department of diagnostics and medical rehabilitation at the SCCH will allow us to demonstrate not only difficulties of etiologic diagnostics of different forms of acute tonsillitis, but also advantages of Streptatest applied by the department's doctors.

Clinical case 1
Arina G., 11 years of age. Admitted to the department in the 5^{th} day of fever (up to 39.5^{o}C) with complaints of pain in swallowing, food refusal and weakness. Had been receiving azithromycin in the dosage of 10 mg/kg domiciliary for 3 days (starting from the 2^{nd} day of disease) with no effect, which is why she was hospitalized.
At admission: hyperemia of pharynx, degree II-III of palatine tonsils, off-white tonsillar deposits, intense hyperemia of conjunctivas, nasal congestion, mucous discharge in common nasal passages. At examination: clinical blood analysis: leukocytes – $17.9x10^{9}$/l, neutrophils – $14x10^{9}$/l, monocytes – 3%, ESR – 40 mm/h, CRP – 270 mg/l, PCT – 1.87 ng/ml, ASLO < 25 IU/ml. Streptatest – negative; cultural analysis – negative.
Given the presence of intense catarrhal phenomena, severity of the disease, inefficiency of domiciliary antibacterial therapy, we suspected adenoviral etiology of the disease; it was later confirmed by the laboratory analysis [indirect immunofluorescence test: pool I adenovirus (3+)].
However, high level of bacterial inflammation markers did not allow us to rule out extratonsillar etiology of fever. That is why the patient continued receiving amoxicillin/clavulanate antibacterial therapy in the dose of 45 mg/kg per day at the hospital. However, the child remained feverish within 48 hours since the treatment started. The temperature normalized by itself in the 7^{th} day of disease.
The child was discharged with diagnosis "Acute adenoviral infection, severe course".
Particular similarities of clinical presentations of acute tonsillites of different etiology are rather well covered in Russian and foreign publications, as well as results of many studies, which proved unreliability of bacterial inflammation markers as of bacterial infection criteria. This primarily concerns adenoviral and Epstein-Barr viral (EBV) infections [2, 3, 11].

Clinical case 2

Andrey V., 3 years of age, hospitalized in the 2nd day of fever (up to 39.6°C) with complaints of pain in swallowing and food refusal. Domiciliary received only antifebrile agents; however, appearance deposits on palatine tonsils motivated hospitalization.
At admission: hyperemia of pharynx, degree II of palatine tonsils, abundant white confluent tonsillar deposits, conjunctivitis, intense nasal congestion with no discharge. Cervical lymphadenitis, moderato hepatosplenomegaly.
At examination: leukocytes – $22.2x10^9$/l, neutrophils – $13.2x10^9$/l, monocytes – 5%, ESR – 15 mm/h, CRP – 32 mg/l, PCT – 0.44 ng/ml, ASLO < 25 IU/ml. Streptatest – negative.
We suspected infectious mononucleosis on the basis of the typical clinical presentation. Given early period of the disease and potential lack of IgM to EBV in diagnostic titers, we used the polymerase chain reaction (PCR) method and revealed EBV in palatine tonsillar material.
The child received only symptomatic therapy at the department; fever relieved by itself in the 4th day of disease. Discharged with diagnosis "Infectious mononucleosis".
Streptatest conducted domiciliary would have allowed the pediatrician to definitely decide whether prescription of antibacterial therapy is reasonable and avoiding unnecessary hospitalization.

Clinical case 3
Ilya A., 5 years of age, hospitalized in the 2nd day of fever (up to 39.2°C) with complaints of pain in swallowing. Deposits on palatine tonsils and fever from the first day of disease motivated domiciliary prescription of amoxicillin/clavulanate in the dosage of 20 mg/kg per day; however, the child was hospitalized due to the lack of positive effect. At admission: hyperemia of pharynx, degree III of palatine tonsils, abundant white confluent tonsillar deposits, sharp nasal respiratory obstruction with no discharge. Increase in the size of cervical lymph nodes up to 3 cm, of liver - +3.5 cm off the costal margin, spleen - +2 cm. At examination: clinical blood analysis: leukocytes – $16.4x10^9$/l, neutrophils – $9x10^9$/l, monocytes – 9%, ESR – 22 mm/h, CRP – 28 mg/l, PCT – 0.5 ng/ml, ASLO < 5 IU/ml. Streptatest – negative.
Typical clinical presentation left no room to doubt the diagnosis. Infectious mononucleosis was confirmed by EBV detection (PCR method) in tonsillar material as well.
The child received only symptomatic therapy at the department; fever relieved by itself in the 5th day of disease. Abundant maculopapular cyanotic-pink rash without pruritus (amoxicillin rash) appeared on skin of the child's body, face and limbs.
The child was discharged with diagnosis "Infectious mononucleosis. Toxic allergic reaction to amoxicillin."
If the patient had undergone Streptatest outpatiently, it would have probably been reasonable to avoid prescription of antibacterial therapy, unnecessary hospitalization and development of unfavorable complications (in the form of exanthema).

Clinical case 4
Evelina O., 13 years of age, admitted to the department in the 5th day of fever (up to 39°C) with complaints of pain in swallowing. Domiciliary received only antifebrile agents.
At admission: hyperemia of pharynx, degree II of palatine tonsils, white tonsillar deposits, cervical lymphadenitis. No catarrhal phenomena.
At examination: clinical blood analysis: leukocytes – $14x10^9$/l, neutrophils – $9x10^9$/l, monocytes – 9%, ESR – 36 mm/h, CRP – 29.2 mg/l, PCT – 0.6 ng/ml, ASLO – 126 IU/ml.
Given the fact that the girl was an adolescent with no catarrhal phenomena, streptococcal etiology of acute tonsillitis may have been suspected with high probability. The only analysis – Streptatest – with positive result allowed diagnosing acute streptococcal tonsillitis within the first minutes of the child's hospitalization and prescribing systemic antibacterial therapy. The fever relieved in the 1st day of treatment.
Cultural analysis conducted along with Streptatest (in the framework of scientific research) confirmed the obtained express test result and revealed heavy growth of *S. pyogenes*.

Domiciliary diagnostics in this case would not only have allowed avoiding hospitalization, but also starting the necessary treatment in the early period of the disease.
Several published works contain recommendations on conducting express diagnostics for the second time in case of a negative result and on the possibility of conducting bacteriological analysis in case of high probability of streptococcal infection with negative express test result [8]. At present, we almost never conduct the control bacteriological analysis at our clinic due to the accumulated experience that allows us to see an extremely high reliability of the used express test, and on the basis of foreign studies [9, 12] featuring high levels of specificity and negative predictive value of the current express GABHS diagnostics.

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