DOI: 10.17816/KMJ2020-805

Clinical efficacy of a screening approach to the differentiated prescription of antibiotic therapy in children with acute tonsilopharyngitis

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Abstract

Aim. To assess the effectiveness of the screening approach by prescribing a streptotest to verify the etiological cause of tonsillopharyngitis in children.

Methods. We observed 67 patients aged 7 to 11 with a history of recurrent respiratory infections. The incidence of acute respiratory infections varied from 8 to 12 times during the year preceding the examination. The main group consisted of 36 children who had tonsillopharyngitis with severe inflammation of the tonsils and plaque on the tonsils. The control group included 31 patients with acute tonsillopharyngitis with inflammatory changes in the tonsils and the absence of plaque. The observation and control groups were comparable and did not have statistically significant differences in gender and age. All patients underwent a common clinical, laboratory, and instrumental examination. Along with microbial culture, the special examinations included an express test (Dectra Pharm, France) for the presence of group A β-hemolytic streptococcus.

Results. All children underwent an etiological examination. The presence of a viral antigen was confirmed in 71.64% of children. 27.49% of patients in the control group and 30.72% of patients in the main group had positive results of the express test for group A β-hemolytic streptococcus, taking into account the requirements for assessing this reaction. It was revealed a reliable direct relationship between the detected viral infection and the negative results of the streptatest test (r=0.86; p=0.03) for the control group, and a positive correlation of the confirmed presence of group A β-hemolytic streptococcus in the main group as with both C-reactive protein (r=0.78; p=0.04) and with inflammatory markers in the general blood test. A combination of positive fluorescence of viral antigens based on the results of immunofluorescence and a positive enzyme-linked immunosorbent assay (ELISA) for group A β-hemolytic streptococcus was recorded in 7.46% of all patients. Clinical examples are given the justification of practical implementation of the express test for the quick diagnostic information.

Conclusion. Differentiated etiological diagnosis of acute tonsillopharyngitis based on clinical symptoms and the levels of markers of bacterial inflammation is extremely difficult therefore laboratory criteria should be the justification for prescribing antibiotic therapy; currently, the most accessible is the streptatest for the detection of group A β-hemolytic streptococcus, which allows confirming or denying the presence of group A β-hemolytic streptococcus within a few minutes, which means that it is correct to prescribe antibacterial drugs to patients.

Keywords: children, streptatest, acute tonsillopharyngitis.

For citation: Pikuza O.I., Zakirova A.M., Moroz T.B. Clinical efficacy of a screening approach to the differentiated prescription of antibiotic therapy in children with acute tonsilopharyngitis. *Kazan Medical Journal.* 2020; 101 (6): 805–811. DOI: 10.17816/KMJ2020-805.

Background. Infectious pathology of the respiratory system is one of the most significant pediatric morbidity, which accounts for 68%–72% of the cases [1,2]. Children most commonly visit the hospital due to upper respiratory tract infections, in particular acute tonsillopharyngitis (ATP). The speculated etiological factor of ATP in pediatric patients is group A β-hemolytic streptococcus (ABHS), which is registered in 30%–40% of the cases, as well as viruses in 60%–80% of the cases [3,4].

Regardless of the etiological factor, clinical symptoms of ATP include an increase in body temperature >38.3°C, sore throat, changes in the mucous membrane of the pharynx, lymphadenitis, impaired appetite, difficulty breathing or swallowing, as well as temporary aphony [5].

For correspondence: azakirova@gmail.com Received 22.06.2020; accepted 14.09.2020.

Causes of sore throat depend on the child's age, season, and climate. The most common symptom of ATP in pediatric patients is intoxication. Body temperature during ATP does not correlate with the etiological factor, and its increase is noted in both bacterial and viral variants [6]. In addition, clinical signs such as fever and plaque on the tonsils are equally common in both bacterial and viral forms of tonsillitis, which complicates significantly the diagnostics [7]. Moreover, bacteria caused complications, such as purulent (e.g., pharyngeal abscesses of various localization, purulent lymphadenitis) and systemic infections (e.g., acute rheumatic fever, post-streptococcal reactive arthritis, streptococcal toxic shock syndrome, PANDAS syndrome[1], and acute post-streptococcal glomerulonephritis) [8].

All these complications necessitate the search for new approaches to differentiate the etiological cause of ATP and, consequently, to prescribe antibiotics according to indications [9]. The frequency of unjustified use of antibacterial drugs for acute respiratory diseases in Russia is approximately 70%. According to the World Health Organization, up to 75% of antimicrobial agents are used irrationally worldwide [10].

Currently, the International Classification of Diseases, 10th edition, which rationally divides acute tonsillitis and pharyngitis into streptococcal and non-streptococcal ones, serves as guidance for medical practitioners. For this reason, the doctor needs to identify the etiology of the disease to make a diagnosis. Every fifth patient with ATP is a carrier of ABHS, a serious bacterial pathogen, which is considered an absolute indication for antibiotic therapy [11]. Only the eradication of streptococcus in the complex therapy of ATP prevents the chronicity of the process, complications, and fatal outcomes, as well as development of resistance [12].

To differentiate ATP of a viral nature from streptococcal ATP by clinical signs, some guidelines suggest the use of the Sentor and MacIsaac scales [13, 14], which helps determine the probability of the streptococcal etiology of ATP. The predictive power of the clinical scales is not high enough, for example, with the maximum score on the MacIsaac scale, the probability is slightly more than 50%. Therefore, even if the patient has the highest score, it is impossible to diagnose streptococcal ATP confidently. According to experts from the Infectious Diseases Society of America, the use of scales and algorithms for identifying patients with a probable streptococcal etiology of ATP leads to an unjustifiably wide prescription of antibacterial drugs [8]. Therefore, laboratory diagnosis is required to establish the streptococcal etiology of the disease and to resolve issues on the indications of systemic antibiotic therapy.

The gold standard for the etiological diagnosis of ABHS infection is the culture-based study of smears from the oropharynx [15, 16]. This method has a sensitivity of 90%–95%, which is subject to correct observance of all conditions for the collection of biomaterials from the tonsils and posterior pharyngeal wall, as well as transportation and incubation. However, the complexity of collection and safety of the material, as well as the early use of antibiotics for ATP, reduce significantly the probability of streptococcus inoculation and limit the use of this method in medicine.

Given the difficulties of a culture-based study, as well as its high cost, rapid tests for the detection of ABHS have become widely known. To date, the sensitivity of rapid tests has reached 95%, with specificity of nearly 100%. Currently, this finding does not require a control bacteriological study [17].

The main advantage of tests for rapid diagnosis is related to the promptness of obtaining results. In addition, their compactness and ease of implementation help identify the etiology of tonsillitis in the doctor's office or directly at the patient's bedside. This is beneficial not only for the patient himself, who can be given an accurate diagnosis within a few min and prescribed reasonable antibiotic therapy or only symptomatic therapy, but also for the doctor's image.

Until recently, methods of rapid diagnosis were practically not used in Russia, while they have been used for many years in other countries. The Food and Drug Administration (FDA; the US Federal Service that controls the production, storage, and sale of food products, drugs, and cosmetics) recommends the use of an outpatient rapid test for the diagnosis of streptococcal infection [18]. Since 2002, the France Ministry of Health has included the use of a rapid test in the antibiotic resistance program, after which the utilization rate of antibiotics has decreased by 50%.

One of the rapid tests registered in the Russian Federation is the Streptatest (Dectra Pharm, France). The Streptatest diagnostic system is compact and easy to use and comprises whatever is required for analysis. Its use helps confirm or exclude quickly the streptococcal etiology of the disease. As a result, the doctor can make a timely rational choice of ATP therapy.

In 2007, leading specialists (such as pediatricians, otorhinolaryngologists, infectious disease

[1] PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) — childhood autoimmune neuropsychiatric disorders associated with streptococcal infections

Table 1. Distribution of the Studied Patients by Sex and Age

Group	Sex		Age, years	
	Boys	Girls	7–9	10–11
Main group, n = 36	17 (47.23%)*	19 (52.77%)*	21 (58.34%)*	15 (41.66%)*
Control group, n = 31	16 (51.62%)	15 (48.38%)	17 (54.84%)	14 (45.16%)

Note: *$p > 0.05$ compared with control.

specialists, and clinical pharmacologists) in Russia developed an algorithm for the diagnosis of ATP in children, which provides the use of rapid tests [19]. The use of systemic antibiotic therapy in ATP is absolutely indicated in the detection of ABHS as well as other bacterial agents.

Our experience of using Streptatest in the detection of ABHS in ATP in pediatric patients with recurrent respiratory diseases is given below.

This study aimed to assess the efficiency of the screening approach by prescribing a Streptatest to verify the etiological cause of tonsillopharyngitis in pediatric patients.

Material and methods of research. This study was conducted in the pulmonology department of the children's hospital of the Central City Clinical Hospital No. 18 in Kazan and the Central Research Laboratory of the Kazan State Medical University. A screening approach for ABHS is included in the standard examination of a child with tonsillopharyngitis.

The study included 67 patients aged 7–11 years with a history of recurrent respiratory infections. The incidence of acute respiratory diseases varied from 8 to 12 times during the year preceding the examination. The main group consisted of 36 pediatric patients who had ATP with manifestations of severe inflammation and plaque on the tonsils, edema, and bright hyperemia. The control group included 31 patients with ATP accompanied with hyperemia but without plaque (Table 1).

All patients underwent thorough clinical, laboratory, and instrumental examinations, which included assessment of the somatic status, biochemical blood test, ultrasonography to identify the probability of urinary system damage, as well as electrocardiography and, in some cases, Holter monitoring to determine organic damage to the cardiovascular system. Along with the microbial culture study, special examination using a rapid test to detect the presence of ABHS was performed.

Essence of the method and its conduct: A tongue-holding forceps should be used to press the tongue down to prevent the saliva from contaminating the special swab. A smear should be taken from the tonsils, throat, and all inflamed, ulcerative, or exudative areas. The test must be performed immediately after taking a smear. If this cannot be done immediately, smear samples can be stored for 4 h at room temperature (15°C–30°C) in a dry, sterile, and hermetically sealed container, or for 24 h in a refrigerator (2°C–8°C). If another culture test is required at the same time, a new swab should be used.

The test strip should be taken from the bag immediately before testing. Pour 4 drops of pink extraction reagent A into an extraction tube and add 4 drops of colorless extraction reagent B. Shake the tube slightly to mix the two solutions. The mixture will change its color from pink to colorless. Dip the swab into the test tube. Twist the swab approximately 10 times in the extraction solution. Leave it for 1 min. Squeeze the swab against the sides of the tube to remove any excess liquid. Throw away the swab. Place the test strip in the extraction tube with the arrows pointing toward the extraction solution. Leave the test strip in the tube. After 5 min, the result can be read.

If the concentration of the infectious agent is high, then a positive result may appear in the first min. However, to confirm a negative result, wait for 5 min. Results obtained after 10 min should be rejected. The result is considered positive when two purple colored bands are displayed in the control and test zones. A negative result is recorded when only one purple band is displayed in the control zone. If no bands appear in the control and test zones, then the analysis was performed incorrectly. In this case, the procedure should be repeated.

The etiology of the disease was established in the laboratories of the A.A. Smorodintsev Scientific Research Institute of Influenza by the immunofluorescent method for the detection of viral antigens in the epithelium of the nasal passages using standard fluorescent antibody preparations obtained at the enterprise for the production of diagnostic preparations at the A.A. Smorodintsev Scientific Research Institute of Influenza, as well as serologically in the reaction of complement binding, hemagglutination–inhibition reaction, indirect hemagglutination test, and enzyme immunoassay. Fluorescent immunoglobulins were used against influenza viruses A2 and B, parainfluenza, respiratory syncytial, rhino- and adenoviruses, and *Mycoplasma pneumoniae.*

Table 2. Distribution of Patients by Etiological Factor

Etiological agent	Main group	Control group
Adenoviral	24.14%*	24.78%
Respiratory syncytial	27.26%*	29.03%
Parainfluenza	7.34%*	7.69%
Rhinovirus	12.04%*	11.12%
Combined viral antigens	13.68%*	13.22%
ABHS	30.72%*	27.49%
Adenoviral and ABHS	7.89%*	7.27%

Note: *$p > 0.05$ compared with control; ABHS, group A β-hemolytic streptococcus.

Table 3. Comparative Analysis between Indicators of C-reactive Protein (CRP) and Inflammatory Changes in the Complete Blood Count (CBC) in the Presence of Confirmed Group A β-Hemolytic Streptococcus

CRP/CBC parameter	Main group	Control group
Erythrocyte sedimentation rate	r =0.82	p = 0.034
Leukocytes, $\times 10^9$/L	r = 0.68	p = 0.046
Stab neutrophils, $\times 10^9$/L	r = 0.77	p = 0.025
Segmented neutrophils, $\times 10^9$/L	r = 0.73	p = 0.042

Statistical processing of the results was performed using the Microsoft Excel 2010 program, with processing of the variation series and calculation of arithmetic mean values, mean error, and indicators of the reliability of differences according to Student's test. To calculate the degree of the relationship between the calculated indicators, the Pearson correlation coefficient was determined. Along with this, to ensure objectivity of the results, individual analysis of digital data, presented as a percentage, was widely performed.

Results and discussion. All pediatric patients underwent etiological examination. The presence of a viral antigen was confirmed in 71.64% of the pediatric patients, including adenoviral antigen in 24.46%, respiratory syncytial in 28.14%, parainfluenza in 7.53%, and rhinovirus in 11.51%, and combined viral antigens in 13.43% of the children (Table 2).

Along with the verification of viral agents, all pediatric patients were examined for the presence of ABHS using Streptatest at the initial examination in the admission ward on day 1 of hospitalization. In 58.21% of the cases, both groups showed positive results of the ABHS test, taking into account the requirements for assessing this reaction.

In the control group, the correlation analysis presented a significant relationship between the diagnosed viral infection and the negative results of Streptatest ($r = 0.86$; $p = 0.03$). A significant direct correlation was found between the indicators of C-reactive protein and inflammatory changes in the general blood test with the ABHS confirmed ($r = 0.78$; $p = 0.04$) (Table 3).

In 7.46% of the cases, a combination of both positive fluorescence according to the results of immunofluorescence and ABHS carriage was registered in both groups (7.38% and 7.53% in the main and control groups, respectively). Moreover, combination of adenovirus and ABHS was most common. Thus, when the patient is already at the admission ward, the doctor determined the exact indications for antibiotic therapy for each case. This is all more important under conditions of hospital operation according to medical and economic standards and to reduce the antibacterial load on the patient.

A clinical case is presented below. This case enables visual assessment of the benefits of Streptatest for diagnosis of various forms of ATP.

Clinical example of the need for rapid diagnosis at the primary care facility to justify the early start of antibiotic therapy and inexpediency of hospitalization. Patient N (14 years old) was hospitalized in the department on day 6 of illness with complaints of fever up to 38.9°C and sore throat when swallowing. He took antipyretic drugs on an outpatient basis. Clinician's findings on admission included hyperemia of the throat, enlargement of the palatine tonsils up to the second degree, white plaque on the tonsils, and enlargement of cervical lymph nodes.

During laboratory examination, general blood test results were as follows: leukocytes, 14.5×10^9/l; neutrophils, 9.4×10^9/l; monocytes, 8%; erythrocyte sedimentation rate, 34 mm/h; C-reactive protein, 28.7 mg/l; procalcitonin, 0.63 ng/ml; anti-streptolysin 0, 122 IU/ml. The Streptatest result was positive. The microbial culture revealed abundant growth of *S. pyogenes*. The prescribed systemic antibiotic therapy contributed to the relief of fever on day 1 of treatment.

Our research experience and the clinical example presented show comparable results of the culture method and Streptatest. To date, the sensitivity of the gold standard is 90%–95%, provided that all conditions for sampling biomaterial from the tonsils and the posterior pharyngeal wall, transportation, and incubation are observed. As regards the Streptatest, its sensitivity and specificity are similar at 95% and 100%, respectively [20], which is one of its main advantages, along with the swiftness of

obtaining results. This justifies the high reliability of the results and avoids the necessity for a control bacteriological study, which is consistent with literature data [20].

Thus, Streptatest, being a highly sensitive and accurate method for detecting ABHS, can be widely used, according to our observations, in ATP in pediatric patients as an alternative to the classical microbial culture study in an outpatient-polyclinic network.

CONCLUSIONS

1. Differentiated etiological diagnosis of ATP in pediatric patients is extremely difficult on the basis of clinical symptoms and the level of markers of bacterial inflammation; therefore, laboratory criteria should be used to determine indications for antibiotic therapy.

2. Given the difficulties of performing a culture-based study of materials from the palatine tonsils, Streptatest is currently the most accessible method for detecting ABHS, which helps identify or rule out the presence of β-hemolytic streptococcus within a few min and, therefore, prescribe correct antibacterial drugs to patients.

Author contributions. O.I.P. was responsible for the analysis of the results and their interpretation. A.M.Z. and T.B.M. conducted research and were responsible for collecting results.

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

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