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Diagnostics and therapy of acute streptococcal tonsillopharyngitis: modern recommendations

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The article dwells upon modern principles of diagnostics and therapy of acute tonsillopharyngitis in children given Russian antibiotic resistance peculiarities of Streptococcus pyogenes. The rate of antibiotic prescription in the event of acute tonsillopharyngitis remains unreasonably high in Russia. The disease most often has viral etiology and antibiotic prescription in such a situation is unreasonable. Prescription of systemic antibiotics is indicated only in the event of the confirmed streptococcal etiology of acute tonsillopharyngitis. Use of the express test in routine practice allows confirming or ruling out streptococcal etiology of the disease quickly and effectively; this allows selecting therapy of acute tonsillopharyngitis timely and rationally.
Keywords: *children, acute tonsillopharyngitis, diagnostics, Streptococcus pyogenes, express test.*

A problem of microbial resistance to antibacterial drugs remains relevant all around the world. Irrational use of antibiotics is conductive of selection of resistant microbes, disturbs normal nasopharyngeal and intestinal biocoenosis [1, 2] and may trigger development of allergic diseases [3].
World Health Organization (WHO) experts earnestly worry about the problem of too widespread use of antibiotics; this reflected in the adoption of a global strategy for containment of antimicrobial resistance in 2001 [4]. In cooperation with the International Fund for Maternity and Childhood Health Protection, the Union of Pediatricians of Russia designed program "Acute respiratory diseases in children: treatment and prevention" in order to rationalize approaches to treatment of acute respiratory infections in children in 2004 [5].
Acute tonsillopharyngitis (ATP) is one of the most widespread infectious diseases in outpatient practice; it is an acute inflammation of the pharyngeal ring's lymphoid tissue (primarily of palatal tonsils) and pharyngeal mucous tunic. Acute tonsillopharyngitis takes at least 15% in the structure of acute respiratory infections [6]. In the USA, pediatricians and general practitioners perform ca. 15 mn consultations due to throat ache every year [7].
Etiology of acute tonsillopharyngites may be either viral or bacterial. In most cases, viruses are the main causative factor of tonsillopharyngitis in children and adults. ATP may develop in the setting of infection with adenoviruses, rhinoviruses, coronaviruses, influenza, parainfluenza, Epstein-Barr, Coxsackie viruses etc. [8]. Acute viral tonsillopharyngites do not require antibacterial therapy [9].
The leading position among bacterial ATP causative agents both in terms of detection rate and severity of the caused complications is taken by *Streptococcus pyogenes* (group A β-hemolytic streptococcus, GABHS). GABHS detection rate in the event of acute tonsillites is 5-15% in adults and 30-43% of children (according to different researchers) [10-12].
Apart from S. pyogenes, such bacterial agents as serogroup C and G streptococci and "atypical" causative agents (*Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*) may be revealed in

throat swabs in the event of acute tonsillopharyngitis. However, their etiological role in the genesis of tonsillopharyngitis has not been fully established. Possible involvement of these microbes as independent causative agents or as copathogens and their possible role in recurrence of ATP symptoms is disputed. Given the aforementioned, neither modern guideline on the treatment of tonsillopharyngites recommends antibacterial therapy in the event of the ATP caused not by GABH-streptococci or "atypical" bacteria [13].

Acute tonsillopharyngitis is usually characterized by acute onset accompanied by body temperature increase and condition aggravation, abdominal pain and symptoms of intoxication. Children often experience abdominal pain, nausea and emesis [14].

The examination reveals hyperemia, edematous tonsils and the pharyngeal posterior wall's mucous tunic, pharyngeal posterior wall's follicular granulosity, purulent tonsillar deposit, enlargement and tenderness of regional anterior cervical and submandibular lymph nodes. However, not all of these symptoms may be present in patients.

Given clinical data exclusively, it is not often possible to differentiate viral acute tonsillopharyngitis from streptococcal tonsillopharyngitis.

Although there are no specific symptoms, which would allow ruling out of confirming diagnosis "streptococcal tonsillopharyngitis", several most significant symptoms for differential diagnostics of GABHS-tonsillopharyngitis ought to be emphasized.

Clinical symptoms of GABHS-tonsillopharyngitis

- acute disease onset;
- pyretic fever (over 38 ^{o}C) from the first day of disease;
- edematous tonsils and exudate in tonsils;
- tenderness of cervical lymph nodes;
- no cough;
- no rhinorrhea.

It ought to be mentioned that even experienced doctors may encounter difficulties related to differential diagnostics considering clinical symptoms only.

Table 1. McIsaac score [16]

Criterion	Score
Body temperature >38^{o}C	1
No cough	1
Enlargement and tenderness of cervical lymph nodes	1
Edematous tonsils and exudate	1
Age, in years	
3-14	1
15-44	0
45 or more	-1

In order to distinguish viral tonsillopharyngitis from streptococcal tonsillopharyngitis using clinical symptoms, several guidelines recommend using Centor and McIsaac score [15, 16], which allow determining probability of streptococcal (GABHS) ATP etiology. McIsaac score is the most widespread score in pediatrics (tb. 1, 2); it offers a management algorithm for patients with symptom "throat ache". It is advisable to evaluate symptoms using a rating score first, and then match the number of points with the probability of streptococcal infection in a patient.

It ought to be mentioned that predictive power of clinical scores is not strong enough: thus, the maximum McIsaac score evaluation renders probability of slightly more than 50%, which is why it is impossible to establish diagnosis "streptococcal (GABHS) tonsillopharyngitis" for sure even if then number of points is high. According to the Infectious Diseases Society of America experts, use of scores and algorithms for singling out patients with probable streptococcal etiology of tonsillopharyngitis results in an unreasonably frequent prescription of antibacterial drugs [17]. As has already been mentioned, clinical symptoms of streptococcal tonsillopharyngitis are non-specific, which is why laboratory diagnostics is required to determine

streptococcal etiology of the disease and decide whether or not to start systemic antibiotic therapy.

Table 2. McIsaac score interpretation

Number of points	GABHS infection risk, in %	Tactics
0-1	5-10	No need in further examination and treatment.
2-3	28-35	Bacteriological smear analysis, antimicrobial therapy in the event of the positive result
>4	51-53	Empirical treatment (in case of pyretic fever, severe general conditions and recent onset) or microbiological diagnostics

Cultural analysis of oropharyngeal smears is the "gold standard" of etiological diagnostics of GABHS-infection. Sensitivity of this method is 90-95% in the event of correct observation of all conditions of tonsillar and posterior pharyngeal wall's biomaterial sampling, transportation and incubation.

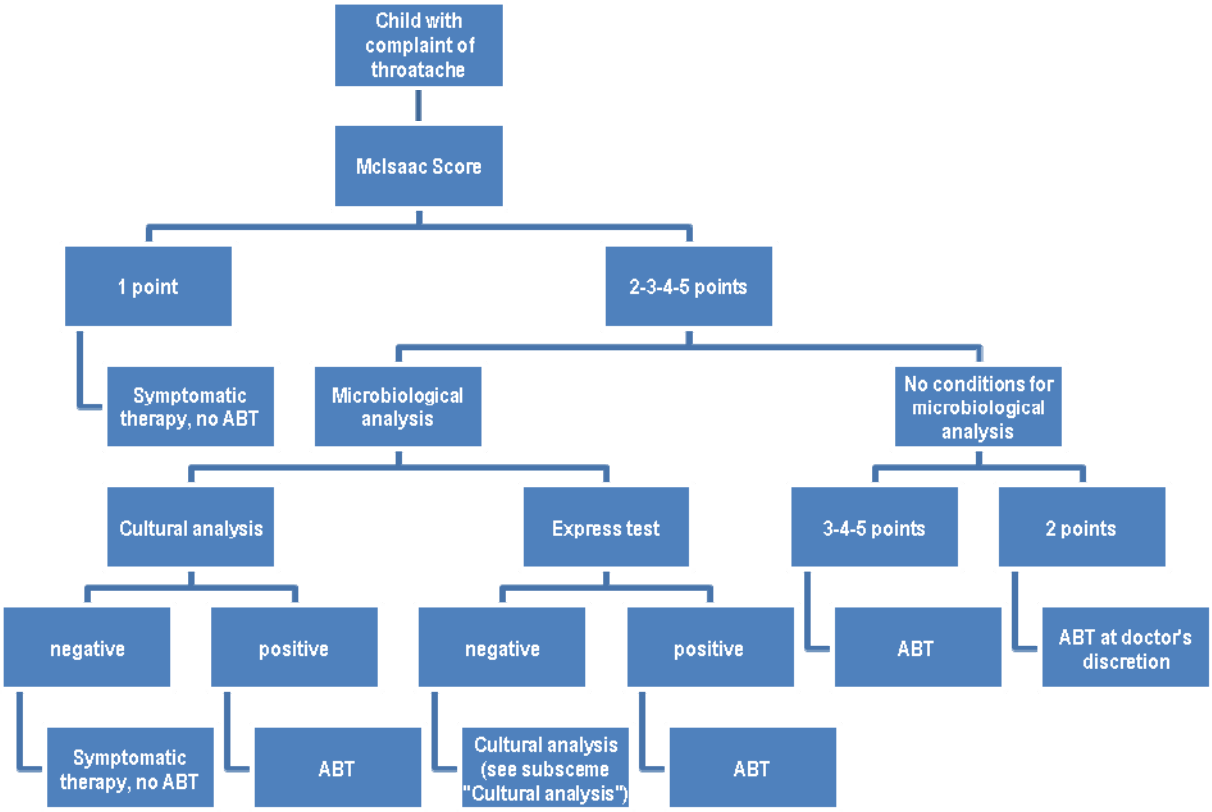
Materials ought to be sampled directly from the surface of tonsils and posterior pharyngeal wall with a sterile cotton wool wad without touching tongue, uvula, buccal surfaces and teeth. Biomaterials ought not to remain in transportation conditions for more than 2 hours. It is necessary to deliver to the microbiological laboratory for cultural analysis within this period. Unfortunately, in real outpatient clinical practice it is not often possible to observe all the conditions; this factor directly affects quality of the obtained results. Duration of result generation – at least 24 hours – ought also to be noted; this does not allow timely use of the analysis results.

An alternative to the classic cultural analysis is methods of fast detection of a streptococcal antigen directly in smears from tonsillar and posterior pharyngeal wall's surface. Express diagnostics methods have almost no use in Russia until recently, whereas they have been employed abroad for many years. The U.S. Food and Drug Administration (FDA) recommends using express tests during outpatient consultations for diagnosing streptococcal infection [13]. Ministry of Health of France included the use of express tests in antibiotic resistance fight program in 2002; after that, the use of antibiotics reduced by 50% [13, 18].

The modern test systems based on immunochromatographic method allow obtaining results directly "at the patient's bedside" with high specificity (95-100%) and sensitivity (up to 95%). Their use allows reducing the percentage of error in identification of ATP etiology and frequency of unreasonable prescriptions of antibacterial drugs and starting etiotropic treatment immediately after receiving a GABHS-positive result.

One of the express tests registered in Russia is Streptatest (Dectra Pharm, France). Diagnostic system Streptatest is compact, easy to use and contains all the components required to perform analyses. Its use allows quickly confirming or ruling out streptococcal etiology of the disease. As a result, a doctor is capable of selecting an acute tonsillopharyngitis therapy in time and rationally.

Acute tonsillopharyngitis diagnostics algorithm for children providing for the use of express tests was developed by the leading pediatricians, otolaryngologists, infectious diseases specialists and clinical pharmacologists in 2007 (pic. 1) [19]. Application of systemic antibacterial therapy and ATP is absolutely indicated if GABHS or such extremely rare causative agents as *Corynebacterium diphtheriae* and *Neisseria gonorrheae* are revealed.



Pic. 1. Acute tonsillopharyngitis diagnostics algorithm for children

Antibacterial therapy of acute GABHS-tonsillopharyngitis is aimed at eradication of the causative agent in order to prevent development of both early (parapharyngeal and retropharyngeal abscesses) and late immunosuppressive diseases (acute glomerulonephritis, acute rheumatic fever); moreover, it is also important to prevent spread of the disease [19].

Antibiotic resistance of GABHS has been being researched in Russia since 1999 in the framework of the "Monitoring of antibiotic resistance of pneumococci, Haemophilus and pyogenic streptococci in various regions of Russia" [20].

According to Russian and foreign studies, S. pyogenes steadily maintains high resistance to β-lactam antibiotics – penicillin and cephalosporin drugs.

Unprotected penicillins are recommended as the drug of choice for the ATP caused by β-hemolytic streptococcus. Protected penicillins do not outperform unprotected penicillins with regard to the *in vitro* effect on GABHS.

However, in some cases unprotected penicillins are not clinically efficient when acute tonsillopharyngitis is caused by *S. pyogenes* (sensitive to unprotected penicillins) due to oropharyngeal copathogens capable of producing β-lactamases. Such a situation may take place in case of recurrent acute tonsillopharyngites, exacerbation of chronic tonsillitis and if a child had been undergoing antibacterial therapy against any other disease within 2-3 months before the treatment [19].

Unfortunately, penicillin therapy often fails due to such a prosaic fact as simple failure to comply with doctor's recommendations. It is well known that the required therapy course duration for most drugs (excluding azithromycin and prolonged penicillins) used for GABHS-tonsillites is at least 10 days, whereas only a few patients comply with such a prescription, especially since condition relief is achieved 24-48 hours after beginning of the therapy and many patients fell clinically healthy by the 3rd day of disease.

The issue had gained such a significant acknowledgment that the FDA suggested including the phrase "…omission of eventual intake of the drug or premature termination of the recommended

antibacterial therapy course may be accompanied by treatment efficacy reduction and microbial resistance development risk increase" to the antibacterial drugs package inserts [13].

Several attempts have recently been made to prove efficacy of shorter antibacterial therapy schemes; however, these recommendations have not gained wide acceptance [21].

Despite a steadily high GABHS cephalosporin-sensitivity, it is not advisable to use them as drugs of the first choice in view of several reasons: firstly, due to their higher cost in comparison with penicillins; secondly, due to the increased risk of antibiotic resistance formation in bacteria if cephalosporins are used [22]. Generation I-II cephalosporins may be used as an alternative therapy in patients with non-severe drug allergy to penicillins; however, they must not be used in presence of anaphylactic reactions to penicillins due to high risk of cross-sensitization [21].

The hottest recent discussions among microbiologists and clinicians concerned use macrolide antibiotics and lincosamides at tonsillitis due to significant difference in macrolide-sensitivity of *S. pyogenes* in different countries. Thus, e.g., the GABHS erythromycin-resistance level in China in 1993-1994 was 79.7%, whereas by 2005-2008 the resistance had almost reached 100%. That country oversees the similar situation with regard to clindamycin-sensitivity of pyogenic streptococcus (within the same period, the resistance had risen from 75.4 to 96.9%). Increase in macrolide-resistance of *S. pyogene*s was mentioned in the studies conducted in Canada (Toronto; 7-fold increase in 1997-2001), Greece, Italy and Latvia.

Interestingly, GABHS macrolide-sensitivity may be considerably more favorable in adjacent countries, e.g., the pyogenic streptococcus resistance level in Norway was only 5%; in Korea, which is adjacent to China, the resistance level had even dropped from 44.8% in 2002 to 4.6% in 2009. Such plummeting was caused not only by rationalization of antibacterial therapy, but also by an almost complete extinction of the resistant GABHS strain with emm12 genotype.

According to Russian studies, 99% of pyogenic streptococcus strain during monitoring in 2006-2009 preserved sensitivity to macrolides an lincosamides; this allows us to assume the possibility of using these drugs for therapy of acute tonsillitis. Moreover, it has been emphasized that given the possible resistance mechanisms, 14- and 15-member macrolides (azithromycin, clarithromycin, spiramycin, roxithromycin) may be used as successfully as 16-member macrolides (midecamycin, josamycin) [13].

Throughout 1999-2009, high tetracycline-resistance level of pyogenic streptococci persisted in Russia (45.8% in 1999-2003 and 33.9% in 2007-2009) [20]. Moreover, tetracycline drugs, along with sulfanilamides with co-trimoxazole, do not eradicate GABHS, which is why they ought not to be used for tonsillitis treatment [19]. It is also a mistake to prescribe local antiseptic and antibacterial drugs at acute streptococcal tonsillopharyngitis [19].

GABHS-tonsillopharyngitis therapy schemes given in Russian methodological guidelines "Use of antibiotics in children in outpatient practice" (edited by A.A. Baranov and L.S. Strachunskiy, 2007; tb. 3) do not significantly differ from foreign recommendations of IDSA, AAP and AHA (tb. 4). The differences of the guidelines concern presence of amoxicillin in foreign guidelines and a wider list of macrolides in the Russian guideline [19].

Thus, diagnostics and rational therapy of acute tonsillopharyngites in children is still relevant. Highly accurate GABHS detection screening method Streptatest provides considerable assistance in determination of the disease etiology; it enables doctors to prescribe adequate therapy on the first disease day and reduce unreasonable use of antibacterial drugs at ATP directly "at the patient's bedside" or during an outpatient consultation.

Table 3. Antibacterial drugs and GABHS tonsillopharyngitis treatment modes for children recommended for children [19]

Antibacterial drugs	Dose	Duration	Connection with food intake
Drug of choice			
Phenoxymethylpenicillin*	At body weight <25 kg:	10 days	1 hour AC

	250 mg BID At body weight >25 kg: 500 mg BID		
Alternative drugs			
Benzathine benzylpenicillin**	At body weight <25 kg: 600,000 IU i/m At body weight >25 kg: 1,200,000 IU i/m	Once	-
Cephalexin	15 mg/kg TID	10 days	Regardless of food intake
Cefuroxime axetil	10 mg/kg TID	10 days	With food
Erythromycin***	13,3 mg/kg TID (40 mg/kg)	10 days	1 hour AC
Azithromycin	12 mg/kg OD	5 days	1 hour AC
Clarithromycin	7.5 mg/kg BID	10 days	Regardless of food intake
Roxithromycin	2.5 mg/kg BID	10 days	AC
Midecamycin	25 mg/kg BID	10 days	15 minutes AC
Spiramycin	1,500,000 IU BID	10 days	Regardless of food intake
Lincomycin	10 mg/kg TID	10 days	1-2 hours AC
Clindamycin	6,7 mg/kg TID (20 mg/kg)	10 days	Wash down with plenty of water

Note. * - recommended primarily for the treatment of children, given availability of the drug in the form of suspension; ** - reasonably prescribed at low compliance to intake of antibiotics, rheumatic fever in anamnesis of children under consideration or their closest relatives, unfavorable social and living conditions or streptococcal infection episodes in organized children's groups; *** - higher frequency of drug-induced gastrointestinal tract's reactions in comparison with other macrolides.

Table 4. Recommended antibacterial drugs and acute GABHS tonsillopharyngitis treatment modes [23]

Antibacterial drugs	Dose	Administration mode	Duration
For patients without allergy to penicillins			
Phenoxymethylpenicillin	For children: 400,000 IU (250 mg) BID or TID In adolescents and adults: 400,000 IU (250 mg) QID or 800,000 IU (500 mg) BID	Intake	10 days
Amoxicillin	50 mg/kg OD (maximum daily dose – 1 g) or 25 mg/kg (not more than 500 mg) BID	Intake	10 days
Benzathine benzylpenicillin	For children with body weight <27 kg: 600,000 IU (375 mg) For children with body weight >27 kg, adolescents and adults: 1,200,000 IU (750 mg)	I/m	Once
For patients without allergy to penicillins			
Cephalexin*	20 mg/kg (not more than 500 mg) BID	Intake	10 days
Cefadroxil*	30 mg/kg (not more than 1 g) OD	Intake	10 days

Clindamycin	7 mg/kg (not more than 300 mg) TID	Intake	10 days
Azithromycin	12 mg/kg (maximum daily dose – 500 mg) OD	Intake	5 days
Clarithromycin	7.5 mg/kg (note more than 250 mg) BID	Intake	10 days

Note. * - patients without immediate (type I) allergic reactions to penicillin in anamnesis.

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