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Modern diagnostics and treatment of acute streptococcal pharyngitis and tonsillitis in children and adults

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The article discusses modern principles of diagnostics and treatment of acute streptococcal pharyngitis and tonsillitis in different age groups. It gives recommendations on using an express test for quick and quality diagnostics of infections caused by group A β-hemolytic streptococcus (GABHS) in routine practice. The introduction of recommendations on diagnostic and therapeutic tactics in adult patients into this article allows to resolve issues of managing family cases of GABHS-infection. Adequate conduct of GABHS express tests and rational selection of therapeutic measures at acute pharyngitis and tonsillitis reduces the risk of prescribing ungrounded antimicrobial therapy.

Keywords*: group A β-hemolytic streptococcus, pharyngitis, tonsillitis, express test, diagnostics, treatment, children.*

Pharyngitis and tonsillitis caused by group A β-hemolytic streptococcus (GABHS) are among the frequent upper respiratory infections both in children and adults. Up to 5-15% of adult patients' and 20-30% of children's visits to doctors on the occasion of sore throat are caused by GABHS pharyngitis and tonsillitis [1, 2].

Accurate timely diagnostics of streptococcal pharyngitis and subsequent adequate antibacterial treatment help to prevent acute rheumatic fever and suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis, cervical phlegmon etc.) reduce the infection risk for the exposed people [3]. It should be mentioned that acute pharyngitis and tonsillitis are observed at most upper respiratory infections, while bacterial (GABHS) disease etiology takes place in not more than 20-30% of children and in an even smaller proportion of adults [2]. Symptoms of viral and bacterial pharyngitis and tonsillitis often are the same, so it is

not always possible to differentiate them on the basis of disease clinical presentation only [4]. Aside from very rare other serious pathogens (e.g., *Corynebacterium diphtheria* or *Neisseria gonorrhoeae*), only GABHS pharyngitis and tonsillitis require antimicrobial therapy. Thus, etiological diagnostics of acute GABHS infection is especially important in order to avoid groundless antibacterial treatment.

Despite significant progress in the differentiated prescription of antibiotics at acute pharyngitis and tonsillitis in children and adults, the rate of groundless antimicrobial therapy remains high all over the world and does not significantly differ in the developed foreign countries (up to 68%) and in Russia (up to 71%) [5, 6]. In its turn, unreasonable antibacterial therapy causes the growth of microbial resistance to antibiotics [7].

Recommendations on diagnostics and treatment of GABHS pharyngitis and tonsillitis significantly differ around the world. Comparative analysis of 11 guidelines (6 – from the European countries; 5 – from the USA) shows that there are 2 fundamental approaches to this disease [8]. In a range of countries, primarily in the USA, streptococcal infection is considered from the point of view of its potential danger, thus, requiring accurate etiologic diagnostics and timely therapy. Other recommendations (Canada, a range of the European countries) are less categorical in appraising reasonability of causative agent's verification; they evaluate the risk of acute rheumatic fever, glomerulonephritis and possible complications of acute GABHS pharyngitis as low, regarding it as a self-resolving disease [8]. It is true that complicated forms of this infection are rare in daily clinical practice; however, we believe that "expectant management" should not be adhered to at the verified acute GABHS pharyngitis or tonsillitis. This work is based on the recommendations suggesting prompt diagnostics and adequate antibacterial therapy of GABHS infection both in children and adults. After that, we discuss principles of diagnostics and treatment of GABHS pharyngitis and tonsillitis, based on high levels of evidence [hereinafter referred to as (A) and (B)] at the conduct of systematic research in this area [9].

DIAGNOSTICS OF GABHS PHARYNGITIS AND TONSILLITIS

Clinical and differential diagnostics

Acute GABHS pharyngitis and tonsillitis have their own clinical-epidemiological characteristics (tb. 1) [4, 10]. The disease most often develops in the winter-spring period in people of 5-15 years of age and is accompanied by intoxication symptoms. Presentation of "ignescent" pharynx, sometimes with hemorrhagic palatal enanthema and exudative elements on palatine tonsils, is typical to it [11].

Table 1. Clinical symptoms at acute pharyngitis and tonsillitis: differentiated diagnosis

GABHS pharyngitis and tonsillitis	Viral pharyngitis and tonsillitis
Sudden sore throat	Conjunctivitis
Age of 5-15 years	Laryngitis
Fever>38^{o}C	Hoarseness of voice
Headache, nausea, emesis, stomachache	Cough
Intense hyperemia of tonsils, palatine arches, posterior pharyngeal wall	Rhinitis
Irregular deposits on tonsils	Diarrhea
Petechiae on hard palate	Aphthous stomatitis
Submaxillary lymphadenitis	Viral exanthema
Seasonal character: winter and early spring	-
Contact with a patient with angina	-
Scarlatiniform rash	-

At the same time, differential diagnostics of pharyngitis and tonsillitis etiology is not always possible on the basis of only a clinical presentation [12, 13]: accurate diagnosis requires bacteriological confirmation. Pharyngitis and tonsillitis may be caused by adenoviruses, rhinoviruses, respiratory syncytial virus, influenza and parainfluenza viruses, ECHO and Coxsackie viruses or by herpes simplex virus. Epstein-Barr virus causes clinical symptoms of infectious mononucleosis. Acute pharyngitis may be associated with infections of cytomegalovirus, rubella and measles.

Cultural study is the gold standard of the GABHS infection diagnostics [2, 14]. The method's sensitivity is 90-95% in case all stages of pharyngeal biological sampling and the smear inoculation of blood agar are conducted correctly [15]. Biomaterial should be sampled from tonsils and the posterior pharyngeal wall. Information value of the pharyngeal smear inoculation is reduced due to children's miscooperation and negativism. False-negative result may also be obtained if the patient has already received at least 1 antibiotic dose. Moreover, delay in the result achievement considerably lowers the value of a cultural method. Express tests for etiologic diagnostics of various infections are now used to achieve a result right "at bedside".

Use of express tests to reveal GABHS

Prompt identification of the causative agent allows not only starting the adequate treatment at once and reducing infection risk for the exposed people, but also helps patients to return to their regular lifestyle [16]. Specificity of the modern express tests for diagnostics of GABHS pharyngitis and tonsillitis is 95%, which is comparable to the cultural microbial study [17, 18]. False-positive express test results are very rare; this allows positive selection of treatment tactics in case of a positive result [17-19]. Unfortunately, sensitivity of most modern tests is 70-90% in comparison with the cultural method [17, 18].

Immunochromatographic express tests (Streptatest, Dectra Pharm, France) have been in the most common use in recent years.

Performing Streptatest for express-diagnostics of angina caused by GABHS

A spatula and a special cotton wool tampon must be used both in microbiological sampling and the standard cultural study. The smear is taken directly from tonsils, posterior pharyngeal wall, palatine arches, i.e. from all the inflamed, ulcerous or exudative zones. It is recommended to perform the test right after the smear sampling. If it is not possible, it is allowed to store a biological sample tampon for not more than 4 hours at room temperature in a dry, sterile and hermetically sealed container or for not more than 1 day in a refrigerator.

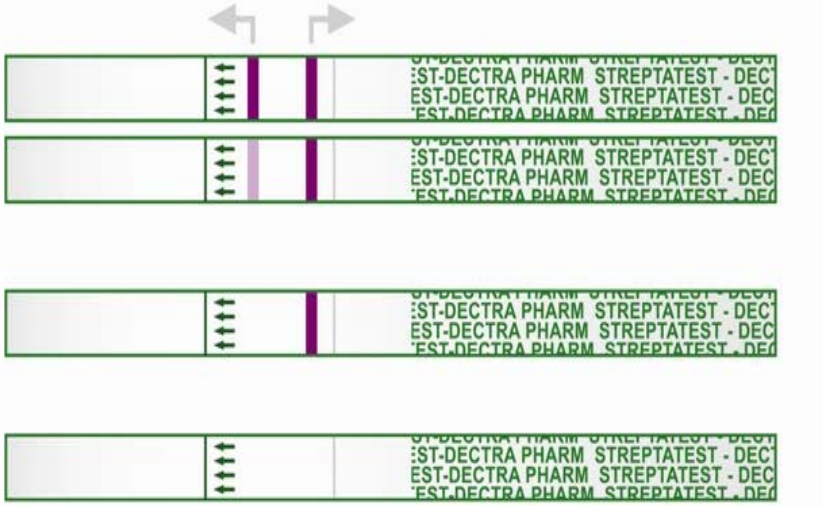
A test strip must be prepared right before the test. 4 drops of reagent A should be poured into the extraction test tube from the test kit; then, 4 drops of reagent B. The solution will change its color from pink to colorless at mixing. A biological sample tampon must be put in the mixture of reagents made in the test tube, turned around ca. 10 times and left for 1 minute. Then, the tampon should be wringed out and may be discarded. A test strip is put in the extraction test tube with the biological sample and reagents in the position determined by the arrows on it. The test strip may be left in the test tube until the end of the test. The result is evaluated 5 minutes after. If the concentration of the infection's causative agent is high, the result may appear already in the 1st minute. It is necessary to wait for 5 minutes to confirm the negative result. The results obtained 10 minutes after the test strip's exposition in the solution should not be taken into consideration.

The evaluation of results is based on the presence or absence of a purple stripe in the test strip's test zone (pic. 1). Appearance of such a stripe indicates a positive result, regardless of the coloring intensity. If such a stripe is absent in the test zone but present in the control zone, the test has been performed correctly and the result is negative. Absence of stripes in both zones when conducting a test indicates its inadequate performance and unfitness for diagnostics.

There is no doubt that the test quality depends on the sample quality. False-negative result may be caused by a bad sample or incompetent smear storing. Negative result may also be obtained in patients on the initial disease stage, who have an insufficient antigen concentration yet. Thus, it is necessary to sample another smear and test it in a cultural study in case there are clinical data for a GABHS infection and the express test's result is negative.

Express tests do not allow quantitative evaluation of the GABHS concentration. In rare cases, samples with large amounts of *Staphylococcus aureus* may yield false-positive results.

Pic. 1. Interpretation of results of an express test for acute GABHS pharyngitis and tonsillitis



Selection of patients for a GABHS express test and cultural study

The risk of acute GABHS pharyngitis and tonsillitis development among adults is higher in case they have school age children [20, 21]. There is an extremely low risk of the rheumatic attack to develop in adulthood, even in case of an undiagnosed and untreated acute streptococcal pharyngitis. Express diagnostics allows making a substantiated decision on the reasonability of antibacterial therapy in case of a clinical presentation of acute GABHS infection in adults [14]. Curiously enough, it is in adults that the excessive use of antibiotics takes place in case of a sore throat [22].

It should be noted that acute GABHS pharyngitis and tonsillitis are often associated with fever, mucopurulent rhinitis and lymphadenopathy in children under 3 years of age, while exudative elements on palatine tonsils are extremely rare. GABHS pharyngitis and tonsillitis usually develop in school age children (up to 37%); in children under 5 years of age its frequency is lower (up to 24%); this reasserts the need in express-diagnostics and cultural studies in these age groups of patients [23]. The spread of acute upper respiratory GABHS infection in children under 3 years of age is appraised at 10-14%, though other data state it does not exceed 6% [24, 25]. Moreover, development of acute rheumatic fever is not typical of children of this age [26]. Children under 5 years of age made up 5% of all patients with acute rheumatic fever; the average age of patients was 4 years. It may be connected with the need in repeated contacts with streptococcal infection for an autoimmune disease to develop [27].

Thus, it is not recommended to test acute pharyngitis's etiology in children under 3 years of age without compelling indications. Presence of the exposed people with acute GABHS

pharyngitis in the family is among such compelling indications. The infection risk of other family members is 25%; there we speak about the risk of a clinically manifesting acute disease, not about the infection carriage [3].

Reasonability of a repeated GABHS test

In case antibacterial therapy is prescribed to a patient with the verified acute GABHS pharyngitis or tonsillitis, clinical response usually develops within the first 24-48 hours of treatment. Even if there is no antimicrobial therapy, streptococcal tonsillopharyngitis resolves without intervention within several days [28, 29]. Longer persistence of symptoms indicates the development of suppurative complications or chronic GABHS carriage. Thus, a repeated GABHS test (both express test and cultural method) for patients, who have been prescribed an adequate antibacterial therapy, is usually unreasonable. The only exception is the patients with high risk of acute rheumatic attack development or the patients with relapsing episodes of GABHS pharyngitis and tonsillitis. Up to 7-37% of children, who have been receiving substantiated and correct antibacterial therapy, have a positive express test (or cultural study result) after the treatment course [30]. Unsuccessful therapy is in most cases connected with GABHS carriage in these patients.

Thus, we may generalize recommendations on diagnostics of acute GABHS pharyngitis and tonsillitis.

Recommendations on diagnostics of acute GABHS pharyngitis and tonsillitis [9]

1. As the clinical presentation does not always allow unambiguous differentiation of GABHS and viral infection, it is necessary to perform an express test to reveal GABHS in pharyngeal smears and/or a cultural study.
2. Viral etiology of pharyngitis is more probable in case of concurrent symptoms of rhinorrhea, cough, microvesicles on palatine arches, aphtae on mouth cavity's mucous tunics and hoarseness of voice.
3. A smear for cultural microbiological study (A) must be sampled in children and adolescents in case of a negative result of the express test.
4. Positive result of the express test does not require a microbiological study, as it is highly specific to GABHS infection (A).
5. Usually, routine examination of pharyngeal smears using a cultural method in adults with a negative result of the GABHS express test is not required, as the risk of GABHS pharyngitis or tonsillitis development in adults is low, while the risk of rheumatic fever development is exceptionally low (B).
6. Study of antistreptococcic antibodies (ASLO) is not recommended for diagnostics of GABHS pharyngitis and tonsillitis, as it does not reflect the acute situation at the moment (A).

The studies of C-reactive protein and leukogram for differential diagnostics of acute GABHS pharyngitis and tonsillitis are not required as well [8, 9].

7. Diagnostic GABHS infection tests are usually not recommended for children under 3 years of age, as the development of rheumatic fever is not peculiar to them and the rate of streptococcal pharyngitis and tonsillitis in this age group is very low. GABHS test may be reasonable in children under 3 years of age in case they have such high-risk factors as, e.g., acute GABHS infection in older brothers and sisters (B).

8. Routine use of express tests or cultural studies is not recommended after the antibacterial treatment has been conducted (A).

9. It is not recommended to conduct diagnostic tests or empirical antibacterial therapy in the asymptomatic people exposed to the patient with acute GABHS pharyngitis or tonsillitis (B).

TREATMENT OF ACUTE GABHS PHARYNGITIS AND TONSILLITIS

Selection of antibiotics

Selection of antibacterial drugs must always be based on the data on their efficacy safety and spectrum broadness, dosage regimen and cost. Many antibiotics are efficient at acute GABHS pharyngitis and tonsillitis: penicillin and its analogs ampicillin and amoxicillin, cephalosporins, macrolides and clindamycin (tb. 2). However, penicillin and amoxicillin remain the drugs of choice, as they are the most efficient, safe and relatively cheap [32]. There have been no publications on penicillin-resistant GABHS strains. Efficiency of peroral amoxicillin intake, which is an optimal introduction mode for this drug, especially in infants, is identical to the efficacy of parenterally introduced penicillin.

Table 2. Antibacterial therapy variants for acute GABHS pharyngitis and tonsillitis [8]

Antibiotic	Dose	Introduction mode	Course duration
For patients without allergy to penicillins			
Penicillin V	Children<27kg: 400,000ea (250mg) BID-TID. Children>27kg, adolescents and adults: 800,000ea (500mg) BID-TID	Ingestion	10 days
Amoxicillin	25mg/kg BID (not more than 1,000mg/day) or 50mg/kg OD (not more than 1,000mg/day)*	Ingestion	10 days
Benzathine/penicillin G	Children<27kg: 600,000ea; children>27kg, adolescents and adults: 1,200,000ea OD	Intramuscularly	Once
For patients allergic to penicillin antibiotics			
Cephalexin**	200mg/kg BID (not more than 500mg per intake)	Ingestion	10 days
Cefadroxil**	30mg/kg OD (not more than 1g per intake)	Ingestion	10 days
Clindamycin	7mg/kg TID (not more than 300mg per intake)	Ingestion	10 days
Azithromycin	10-12mg/kg OD (not more than 500mg)	Ingestion	5 days
Clarithromycin	7.5mg/kg BID (not more than 250mg per intake)	Ingestion	10 days

Note. * - OD amoxicillin dosage regimen has not yet been reproduced in annotations to drugs containing amoxicillin; efficacy of such dosage is confirmed by clinical studies; ** - cephalosporins should not be used in patients anaphylactic to penicillins [31].

The comparative studies demonstrated efficacy of an OD amoxicillin intake at 50mg/kg per day (not more than 1,000mg) for 10 days [33-35]. The OD amoxicillin dosage regimen was stronger adhered to by patients, had low cost and was as efficient as the BID intake of the antibiotic [36]. Possibility of such a prevention course for acute rheumatic fever is stated in many guidelines in the USA; however, it has not yet been approved by the US Food and Drug Administration (FDA).

ATTENTION! Many researchers show that cephalosporins may have higher efficacy in treating GABHS than penicillins [36, 37]; however, there have been no guidelines that would state them as the first choice drugs [8] due to their high cost and high risk of formation of antibiotic-resistant microbes in the process of their application [38]. Cephalosporins substitute amoxicillin at drug allergy to penicillins. However, they should not be used in patients with anaphylactic reactions to penicillin due to high risk of cross sensitivity. Cephalosporins may be seen as an alternative to macrolides in treating acute GABHS pharyngitis and tonsillitis and may also be successfully used at relapsing GABHS infections [8, 9].

It is not recommended to use tetracyclines, as GABHS is resistant to them. Sulfonamides and sulfamethoxazole/trimethoprim do not result in GABHS eradication [39]. The first generation fluoroquinolones have low activity against GABHS, so they should not be prescribed. New drugs of the range are expensive and, even if they very effective, they are not better than cheaper drugs [40]. GABHS resistance to clindamycin does not exceed 1%, and it may be used successfully as an alternative drug, especially in patients allergic and anaphylactic to penicillins and cephalosporins [41]. Resistance to azithromycin is up to 5-8% [41]; however, there are data that a 10-day clarithromycin course is more efficient than a 5-day azithromycin course at acute GABHS pharyngitis [30].

Antibacterial treatment duration

Almost all guidelines on the treatment of acute GABHS tonsillopharyngitis recommend at least a 10-day antibacterial treatment course [8]. The treatment course may be shortened down to 3-6 days in case of low adherence to therapy in children [42]. Literary meta-analysis (Cochrane review, 20 studies, data on 13,102 patients) on the use of shortened treatment courses for acute GABHS pharyngitis and tonsillitis was published in 2009. It demonstrated that a 2-6-day antibacterial therapy course is as effective as a 10-day course in terms of GABHS eradication and a rate of repeated episodes of acute GABHS tonsillopharyngitis [42]. However,

that review received rather critical response in most publications. It did not include several broad studies, which obtained different results; many of the included studies gave unclear randomization criteria of patients, singular studies were double blind; acute rheumatic fever development was not seen as an efficacy criterion [43, 44]. At the same time, a range of authors demonstrated lesser efficacy of short antibiotic acute GABHS pharyngitis therapy courses in terms of clinical symptoms and bacteriological results [45]. 5-day cefdinir, cefpodin and azithromycin treatment courses have been approved in the USA; however, this practice has not received wide use.

Antibiotic introduction mode

Antibiotics at acute GABHS pharyngitis and tonsillitis may be prescribed both *per os* and parenterally. Usually, various peroral amoxicillin forms are used; however, injections may be employed in case of low patients' cooperation and lack of certainty about their ability to complete a full oral treatment course.

Reasonability of antibacterial therapy of people exposed to the patient with acute GABHS tonsillopharyngitis

Asymptomatic GABHS carriage is described in people who have been exposed to patients with acute GABHS pharyngitis and tonsillitis [46]. Studies of antibiotic prevention efficacy in the exposed people showed that preventive penicillin prescription to the family members of the patient with acute GABHS pharyngitis does not prevent the development of acute GABHS infection [34, 47]; low positive effect has been shown in terms of prescription of cephalosporins [48]. As in this case the rate of side reactions at the antibacterial therapy prescription exceeds its benefits, it is unreasonable to prescribe an antibiotic to people who had been exposed to the patient with acute GABHS tonsillopharyngitis for the purpose of prevention.

Antibacterial therapy at GABHS carriage

Routine repeated cultural study is not recommended to those who have had acute GABHS tonsillopharyngitis. Usually, it is the patients with relapsing acute upper respiratory GABHS infection episodes who required repeated etiologic diagnostics (express tests or pharyngeal smear inoculation). In case of the repeated positive GABHS test result, we may assume that patients either have not observed the prescribed treatment or have been infected again by the people with the acute disease that they have been exposed to or they are GABHS carriers. We may not completely rule out the risk of repeated infection by the same GABHS strain; however, such a risk is very low [49].

Chronic GABHS carriers may revealed by the detection of GABHS in pharynx; however, they do not have an immune response to the infection and the titer of antistreptococcic antibodies does not grow [50]. Up to 20% of schoolchildren may be asymptomatic GABHS carriers in

countries with moderate climate in winter and spring. The carriage may remain in place for up to 6 months; usually, children experience at least 1 episode of viral pharyngitis in this period [51]. Many of them are unreasonably prescribed antibiotics. Usually, GABHS carriage does not require antibacterial therapy prescription, as streptococcus almost never transmits to the exposed people from such patients, while the risk of development of suppurative and non-suppurative complications of acute GABHS infection is very low [51]. Moreover, the studies show that it is difficult to achieve GABHS eradication in chronic infection carriers; this is true both for penicillins and other antibiotics [49].

Antimicrobial therapy is not recommended to most chronic GABHS carriers. The treatment is prescribed only in special situations:

1) epidemic eruption of acute rheumatic fever;
2) epidemic eruption of acute GABHS infection in a closed or semi-closed group of people;
3) relatives with rheumatism;
4) families with especially high anxiety towards GABHS infections;
5) when tonsillectomy is planned only due to chronic GABHS carriage.

In these cases therapeutic regimens are slightly different from the standard selection of amoxicillin and penicillin (tb. 3).

Table 3. Therapeutic regiments at chronic GABHS carriage*

Antibiotic	Dose	Course duration	Level of evidence
Peroral antibiotic introduction			
Clindamycin	20-30mg/kg per day in 3 intakes (not more than 300mg/dose)	10 days	A
Penicillin and rifampicin	Penicillin V – 50mg/kg per day in 4 intakes for 10 days (not more than 2,000mg/day). Rifampicin – 20mg/kg OD for 4 days (not more than 600mg/day)	10 days	A
Amoxicillin-clavulanate	40mg/kg of amoxicillin per day in 3 intakes (not more than 2,000mg of amoxicillin per day)	10 days	B
Intramuscularly and perorally			
Benzathine/penicillin G (i/m) + rifampicin (ingestion)	Benzathine/penicillin G – 600,000ea – for children<27kg; 1,200,000ea – for patients>27kg. Rifampicin – 20mg/kg per day in 2 intakes (not more than 600mg/day)	Benzathine/penicillin G – 1 dose; rifampicin – 4 days	A

Note. * - antibacterial therapy is indicated only in rare cases of GABHS carriage (see text).

In case a doctor observes repeated episodes (“ping-pong”) of acute GABHS tonsillopharyngitis in members of one family, a snap GABHS express test or inoculation of pharyngeal smears may be conducted to the whole family with the subsequent prescription of antibacterial therapy to those in whom the test will have a positive result.

Tonsillectomy

Tonsillectomy may be indicated to singular patients with acute episodes of GABHS tonsillopharyngitis, the rate of which does not decrease with time and in situations where there is no alternative variant of treatment. Tonsillectomy was proved efficient only is a small group of patients [52]. Thus, recommendations on the treatment of acute GABHS pharyngitis and tonsillitis may be generalized as follows.

Recommendations on the treatment of GABHS pharyngitis and tonsillitis [8, 9]

1. Patients with acute GABHS pharyngitis and tonsillitis should be prescribed an adequate antibiotic in an adequate dose for the period time sufficient to eradicate the microbe from pharynx (usually, for 10 days). On the basis of the known spectrum, rarity of side reactions and moderate cost, the drugs of choice at present are penicillin or amoxicillin, unless a persona is allergic to these drugs (A).

2. In case a patient is allergic to penicillin antibiotics, the first generation cephalosporins (in case these patients are not anaphylactic to penicillins) may be used for a period of 10 days; clindamycin and clarithromycin may be used for a period of 10 days, azithromycin – for a period of 5 days (A).

3. If needed, antifebrile drugs (A), excluding aspirin in children (B), may be used as an additional therapy.

4. Patients with frequently repeated episodes of laboratory-confirmed GABHS pharyngitis may in fact be GABHS carriers experiencing repeated viral infections (B).

5. It is not recommended to detect GABHS carriers and prescribe antibacterial therapy to them in case there is no clinical presentation of acute GABHS infection, as the infection risk for the exposed people is extremely low, while the risk of development of complications is low (B).

6. It is not recommended to use tonsillectomy to reduce frequency of GABHS pharyngitis (A).

Future studies of diagnostics and treatment of acute GABHS tonsillopharyngitis may be aimed at improving express tests for differentiating between acute infection and carriage, researching efficient short disease therapy regimens and creating an efficient GABHS vaccine.

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