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## **ACUTE RHEUMATIC FEVER: CLINICAL AND DIAGNOSTIC ASPECTS AT THE CURRENT STAGE**

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### **Annotation:**

Today, despite the advances in treatment and prevention, the problem of ARF remains relevant among pediatricians and otolaryngologists. Rheumatic carditis, complicated by ARF, is considered the main reason for hospitalization of patients aged 5 to 24 years in cardiology departments. Worldwide, every year, according to WHO statistics, about 500 thousand people fall ill with rheumatic fever, and in 300 thousand of them, ARF is complicated by the development of heart defects. These complications are the main cause of disability. As we know from foreign literature sources, the etiology of the development of ARF is GAS, but unfortunately the epidemiology of this infection has changed significantly in recent years. Today, the outdated term “rheumatism”, which traditionally previously belonged to the branch of rheumatology, has fallen out of use. And instead of this term, according to the classification, we still use the term “acute rheumatic fever”, which is most justified. The use of the term acute rheumatic fever directs the doctor to clarify the role of GABHS infection in the development of this pathology, and also indicates the need to prescribe antibiotics to eradicate the pathogen in the acute period (primary prevention) and prevent repeated attacks (secondary prevention). According to the ICD-X revision (WHO, Geneva, 1995), ARF belongs to class IX - “diseases of the circulatory system”, presented in headings I00 and I05 as independent groups of diseases and identified as independent nosological forms. This seems justified from the point of view of treatment tactics for patients and to justify primary and secondary prevention.

**Key words:** acute rheumatic fever, secondary prevention, children, modern stage.



### Introduction:

From ancient times we know that one of the oldest diseases of mankind is acute rheumatic fever. In 460-377 BC, Hippocrates described the clinical picture of acute rheumatic arthritis and noted the fact that this disease mainly occurs in young people. Analysis of foreign literature data (Mamedova SN, Musaev SN, 2022) showed that the activation of invasive streptococcal diseases is associated with a change in the pathogen serotypes circulating in the population - M-types 2, 4, 12, 22 and 49 have replaced known as rheumatogenic and toxicogenic M types 1, 3, 5, 6, 14, 18, 19, 24, 28, 29. These changes have led to an increase in the incidence of acute rheumatic fever and toxic infections (scarlet fever, toxic shock syndrome and toxic tonsillopharyngitis) [5,8,9]. WHO in its reports provides data on the high (20–50%) prevalence of GABHS infections among schoolchildren, which explains the potential for the development of ARF in young people predisposed to it.

Titova LV (2023) describes variants of the course of ARF. Buyo-Sokolsky disease or acute rheumatic fever (ARF) is a systemic disease that primarily affects connective tissue localized in the cardiovascular system, joints, brain tissue and skin, caused by group A  $\beta$ -hemolytic streptococcus (GABHS), mainly developing in predisposed individuals, especially young people, from 7 to 15 years of age, due to the body's autoimmune response to streptococcal antigens and cross-reactivity with similar autoantigens of affected human tissues (the phenomenon of molecular mimicry). Also based on this disease is an autoimmune process after pharyngitis, impetigo or scarlet fever caused by group A  $\beta$ -hemolytic streptococcus [5,7,22].

Some authors argue that the epidemiological situation with infectious diseases, including ARF, has worsened all over the world [11,12, 25]. The clinical polymorphism of the disease and the widespread introduction of echocardiography (EchoCG) into widespread clinical practice prompted experts from the American Heart Association to make another revision of the ARF criteria, the results of which were published in May 2015 [13,14,16,19]. The main aspects of the review by the association's experts consist in pointing out the need to determine the risk of developing ARF in each patient, with mandatory consideration and analysis of the epidemiological situation in the region of his residence. The next important criterion for revision is the evidence of a connection between the characteristics of the clinical



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picture of the disease and a previous infection of the pharynx caused by  $\beta$ -HSA, which was confirmed by microbiological or modern immunological methods (ELISA) [15,17,20].

It should be emphasized that to confirm the role of GABHS in the development of ARF, a positive bacterial culture from the throat plays an important role. In modern medicine, serological tests are indispensable to detect elevated or increasing titers of antistreptococcal antibodies - antistreptolysin-O (ASL-O) and antideoxyribonuclease B (anti-DNase B) to diagnose past infection. Many authors describe the main factors in the development of ARF, which is GABHS pharyngitis. It occurs in children much less frequently than the viral one. The incidence of ARF with GABHS pharyngitis is about 3% [1,2].

I would especially like to emphasize the direct significance of the body's autoimmune reaction. The autoimmune reaction that develops with ARF can be activated some time after the onset of pharyngitis. Therefore, to diagnose GABHS infection, it is considered important to consider the classification of Jones criteria. For example, with ARF, all structures of the heart are usually affected, which is reflected in the term "rheumatic carditis," but the term "valvulitis" is of exceptional importance both for diagnosis and for further prognosis. Interstitial granulomas of Aschoff-Talalaev, characteristic of ARF, can be located in the pericardium and can manifest as fibrinoid pericarditis, undergoing reverse development without damage to these structures, but granulomas with valvulitis are usually complicated by valve defects [14,46,47].

In the 20th century, the introduction of echocardiography into clinical practice allowed timely diagnosis of developed cardiac complications, which is why this modern stage is called the "era of echocardiography." In the revision of the 1992 criteria, it was noted that there is insufficient evidence to classify echocardiographic parameters of valvulitis as major criteria [1,4,5]. But according to the latest results of scientific research by Akhrorova FM (2022), an echocardiogram is considered an essential research method to confirm the diagnosis in patients with ARF or suspected ARF, as well as to monitor valvular lesions after ARF [3].

As stated above, the diagnosis of ARF is made based on the revised Jones criteria, which was developed in 1944 by T. Duckett Jones. It was revised in 1992 and 2015



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by the American Heart Association (AHA). In 1944, the classification of ARF proposed by Jones due to the imbalance of overdiagnosis and underdiagnosis causing difficulties for clinicians for some time [1,6,9,10,12].

]. These difficulties prompted a revision in 1995 by the American Heart Association.

Important changes during the revision are as follows:

- firstly, according to risk, the population was divided into moderate, high and low risk groups;
- the diagnosis “subclinical carditis” was added;
- as signs of musculoskeletal inflammation in monoarthritis were introduced in populations with moderate and high risk.

According to numerous literature data (Belov BS, Babaeva AR, 2016), the last revision of these Jones criteria was carried out in 2015. And currently, the diagnosis of ARF is based on the Jones criteria, which include two major and minor manifestations, according to the risk of the population, they are divided into groups: low, intermediate and high risk. The main initial diagnostic criteria include cardiac lesions (carditis), joint lesions (arthritis), central nervous system lesions (chorea), and skin lesions (erythema annulare and subcutaneous nodules). Additional criteria include arthralgia, hyperthermia, elevated ESR, elevated C-reactive protein, and prolonged PQ interval [3,9,11,17,19,20]. If it is assumed that a possible diagnosis of ARF as the first episode of the disease, it is necessary to identify two main criteria or one major and two minor criteria, and for the diagnosis of subsequent episodes of RL, two main criteria or one major and two minor criteria or three minor criteria must be identified in the patient [9, 10]. To confirm infection with BGS, there must be a positive throat culture for a streptococcal pathogen and an increase in the titer of antistreptolysin O (ASLO). Highlighting the importance of the revised Jones criteria, this is an achievement in improving the diagnosis of ARF. As follows from the data of Yalymova DL et al. (2014) it is advisable to introduce the term “subclinical carditis” and presented EchoCG as criteria for the diagnosis of rheumatic valvulitis [13,14].

According to the studies of the above authors (Yalymova DL et al. 2014), when diagnosing subclinical carditis, as the only main criterion, it is certainly very important to conduct a high-quality echocardiography, the interpretation should be



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carried out by an experienced specialist in this field. WatkinsD. A., JohnsonC. O.etc (2017) admit that the frequency of diagnostic errors may increase significantly[19]. Depending on the structure of the patient's immune system, clinical signs of ARF (chorea, carditis, erythema) appear approximately three weeks after a streptococcal infection of the upper respiratory tract. The most serious complication that often leads to death is carditis, which in turn in the acute period can lead to heart failure and death from pancarditis [1,23]. Analyzing foreign and domestic literature, we did not find information on specific biomarkers that provided complete information about ARF; without any laboratory data and functional studies, it is difficult to assess the activity of the disease at the time of patient admission. Features of the course of ARF and the severity of clinical manifestations primarily depend on the genetic predisposition of the patient himself, as well as on the type of streptococcus, its virulence, living conditions, and of course the population [16,20,23]. According to modern concepts, repeated ARF is not a relapse of the first attack, but is a recurrent disease that occurs after an active  $\beta$ -HS group A infection of the upper respiratory tract [5,6].

Despite advances in the diagnosis of acute rheumatic fever, repeated attacks of ARF and the formation of heart lesions, as well as other complications, are common. Today, research continues to find modern effective methods of diagnosis and treatment [17,18].

It should be emphasized that the body's immune system plays a large role in the pathogenesis of the development of ARF and its transition to rheumatic heart disease. Immune mechanisms decide two aspects: activation of GABHS and predisposition to the development of rheumatism. Not all patients have a streptococcal infection that leads to the development of acute rheumatic fever. And only 3% of those who have recovered from streptococcal infection develop ARF. In families of patients with acute rheumatic fever, the tendency to an increased immune antistreptococcal response (ASL-O, ASH, ASA, DNase B) and the prevalence of ARF and rheumatic heart disease are higher than among first-degree relatives [9,17,20,24].

Currently, there is convincing data from Bushueva EM (2019) that in the development of ARF, the individual increased immune response of the body to



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antigens of streptococcal infection and anti-streptococcal antibodies plays an important role, which determines the duration of this response. The reasons for the long-term persistence of antistreptococcal antibodies and hyperimmune reactions have not yet been clarified and require further research. Research is underway on the role of streptococcal elimination due to genetic mechanisms. In most cases, the pathogen takes the L form, which explains the persistence of this pathogen. Research in the field of molecular genetics proves that the incidence is high among patients with blood groups AO (II), BO (III). There are also a number of studies related to HLA phenotype [16,19].

Thus, there is data on the role and mechanisms of development of acute rheumatic fever and complications, streptococcal infection as an etiological factor of the disease, but the mechanisms of genetic predisposition to this disease have not been fully disclosed [5].

According to research by A likuT. O. (2022), the pathogenesis of the development of clinical manifestations of acute rheumatic fever such as annular erythema, arthritis, rheumatic carditis, chorea is most inclined to inflammation of an immune nature, immunopathological processes where antigens of streptococcal infection and antibodies produced against these antigens play a large role. This pathogenesis also explains the toxic component at the onset of the disease. An autoimmune reaction to streptococcal infection antigens is also possible. A cross-reaction of streptococcal antigens between myocardial antigens was proven, and subsequently a cross-reaction was discovered between the components of the streptococcal membrane and sarcolemmal antigens, streptococci and components of the atrioventricular bundle, streptococcal membranes and cytoplasmic neuronal antigens in children with acute rheumatic chorea. In pathogenesis, immune mechanisms in rheumatic carditis are explained by the detection of circulating antigen-antibody complexes in the blood of patients. According to Tenkova OA, Makarenko EV (2019), the formed immune complexes bind to proteins and antigens of connective tissue, clinically manifested by symptoms of connective tissue damage. This mechanism is the main mechanism in the development of ARF and RHD [3,4,7]. These mechanisms activate cellular and humoral reactions, which in turn lead to structural and functional changes





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[7,9,25]. Activation of autoimmune reactions persists for a long time even after recovery [6,7].

In recent years, scientific research has been conducted in the field of immunology, in particular the study of pro-inflammatory and anti-inflammatory interleukins, which have a huge role in the development of acute rheumatic fever and fibrotic lesions of the heart valves [22].

Biochemical changes subside within 2-4 weeks. It is advisable to evaluate these changes after 2-4 weeks after treatment, although the disease can last up to several months [5].

Thus, it is equally important to study cytokines in the development of acute rheumatic fever. Studies of cytokines have shown that polymorphism of a number of genes is responsible for susceptibility to acute rheumatic fever and valvular damage. Polymorphisms of some genes are capable of encoding autoimmune proteins that activate immune responses. Immunoreactive proteins include tumor necrosis factors, interleukin-1a, cytotoxic T-lymphocyte protein and others.

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