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EDITORIAL
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Controversial and open issues of diagnosis and treatment of myocarditis (based on the discussion of Russian national recommendations)

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In October 2020, the Russian Ministry of Health approved clinical guidelines for the management of patients with myocarditis. The aim of this review was to highlight controversial and open issues without unambiguous answer or those that were not described in the paper. The review highlights the objective factors that complicate the development of practical guidelines for the management of this category of patients. Comments on the definition and classification of inflammatory heart diseases are given. The approaches to the diagnosis of patients with suspected myocarditis are discussed. Particular attention is paid to the decision-making strategy in selecting optimal therapy in patients with documented myocarditis and the role of endomyocardial biopsy.

Keywords: myocarditis, clinical guidelines, open issues, diagnosis, treatment, expert comments.

Relationships and Activities: none.

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The last decades have been marked by numerous clinical and experimental studies, which have significantly changed our understanding of the pathogenesis of inflammatory myocardial diseases and served as the basis for a number of papers outlining the position of experts in the diagnosis and treatment of myocarditis [1-3]. A year ago (in October 2020) the Russian Ministry of Health approved the recommendations of the Russian Society of Cardiology on the myocarditis diagnosis and treatment (full text is available on the website of RSC scardio.ru) [4]. This event was preceded by a long period of discussion and amendments to the text of the recommendations by members of the expert group. In September 2020, the final stage of public discussion of the recommendation text took place at the Russian National Congress of Cardiology, which showed that an acceptable consensus was reached on many issues. However, a number of issues require further discussion.

The problem of myocarditis diagnostics and treatment in the practice of cardiologist, unlike other nosological forms, holds a unique position due to the lack of unambiguous decisions on a number of issues for objective reasons. They are related to the complexity and polyetiology of the pathological process itself, the absence of specific clinical manifestations of the disease, making its pre-test diagnosis difficult, the low availability of intravital endomyocardial biopsy (EMB), required to verify the diagnosis and choose the optimal treatment method, the unfavorable disease prognosis, associated with the development of systolic myocardial dysfunction, life-threatening rhythm and conduction disturbances, against the background of almost complete absence of randomized and, first of all, multicenter clinical trials, confirming the effectiveness and safety of currently available basic treatment methods. The only European document that outlines approaches to the management of patients with myocarditis remains the guideline (Current state of knowledge) 2013, to which we will refer more than once [1].

The year 2020, marked by a new coronavirus infection, has made the problem of myocarditis particularly urgent, bringing into our practice not only a very unique variant of SARS-CoV-2 induced myocarditis, but also new issues related to the management of patients suffering from acute and chronic forms of other etiologies. Thus, the circle of doctors who will be affected by these issues has undoubtedly expanded.

The purpose of this publication is to highlight controversial and unresolved issues that have not been answered unambiguously or have remained outside the scope of the published recommendations. Their final resolution is hardly possible without performing specially designed studies, but we hope that the introduction of domestic recommendations into real clinical practice will contribute to the accumulation of Russian experience and will make the algorithm for managing patients with myocarditis more effective.

Definitions and issues of myocarditis classification. During the discussion, the experts considered at least 5 different definitions of myocarditis, and even more diverse were the variants of classifications. These questions are not peripheral, because they are directly related to clinical practice (making and formulating a diagnosis, which largely determines the choice of treatment in each case).

The text of the recommendations included the following definition: "*Myocarditis — a group concept (a group of independent nosological units or a manifestation of other diseases), myocardial damage of an inflammatory nature, infectious, toxic (including medicinal), allergic, autoimmune or unclear etiology, with a wide spectrum of clinical symptoms: from asymptomatic course, mild shortness of breath and unexpressed pain in the chest, passing on their own, to heart failure, cardiogenic shock, life-threatening rhythm disturbances and sudden cardiac death*"[1]. The definition undoubtedly requires further revision, since myocarditis is not a concept, but "a group of diseases with inflammatory nature of myocardial lesions...". In contrast to the Russian recommendations, the European recommendations define inflammatory myocardial disease based solely on morphological signs (histological, immunological and immunohistochemical confirmation of inflammatory infiltrates in myocardium combined with signs of necrosis and degeneration of cardiomyocytes of non-ischemic genesis), which has several weaknesses: impossibility of diagnosis in patients with a mild course of the disease, in which EMB is not indicated, as well as difficulty in interpreting biopsy findings in comorbid patients (for example, ischemic damage of cardiomyocytes with secondary inflammatory reaction can not always be excluded). All of the above factors can make adjustments in the incidence and prevalence of myocarditis in the general population. On the contrary, the definition given in the Russian recommendations includes all basic characteristics (etiology, pathogenesis, clinical presentation, outcomes) of inflammatory myocardial disease and in general better meets the objectives of real clinical practice. However, the absence of morphological confirmation of the diagnosis can, on the one hand, lead to overdiagnosis of myocarditis, and on the other hand, make it difficult to decide on the prescription of specific therapy.

[1] Further, all quotations from the text of the national recommendations on myocarditis will be given in italics.

Along with the definition of various variants of myocarditis, the Russian recommendations provide an interpretation of other definitions that are widely used in English-language literature. In particular, the concept meaning of "inflammatory cardiomyopathy" as "myocarditis with myocardial dysfunction" is explained. Initially, this term reflected the stage of inflammatory myocardial damage with development of structural and functional changes characteristic of both acute and chronic myocarditis. However, if we turn to the definition of dilated cardiomyopathy (DCM) as left ventricular dilatation or biventricular dilatation with development of systolic dysfunction in the absence of risk factors (hypertension, valve pathology, ischemic heart disease), explaining impaired global myocardial contractility, we see that making a differential diagnosis between these similar in clinical manifestations nosological forms is impossible without performing EMB. In turn, confirmation of morphological criteria of active inflammation of non-ischemic nature forces us to make a diagnosis of acute or chronic myocarditis, which from a practical point of view will allow to discuss the prospects of specific therapy. Thus, the use of the term "inflammatory cardiomyopathy", which can be classified under ICD-10 headings I.42.8 (other cardiomyopathies) or I.42.9 (unspecified cardiomyopathy), does not significantly affect the management of a patient with recent myocardial systolic dysfunction, which traditionally is treated as DCM as a clinical diagnosis by practicing doctors until modern research methods are applied. In addition, it has been shown that previously silent recessive defects in genes not related to immunity but encoding the synthesis of cardiomyocyte structural proteins responsible for the development of cardiomyopathies increase susceptibility to viral infection as the most frequent cause of myocarditis [5]. This fact only confirms the theory of J. F. Goodwin on the polyethological nature of DCM syndrome [3, 6].

The issues of myocarditis classification cannot be considered secondary, because it is it that systematizes the doctor's thinking and largely determines the approaches to diagnosis and treatment. At the same time, there is no unified classification of myocarditis, which would meet the clinical requirements and make it possible to choose the optimal management tactics. This is probably why classification is one of the weakest points in the presented recommendations. Unfortunately, the Mayo Clinic classification, which emphasizes the nature of disease course depending on the variants of myocardial debut, and the clearly outdated clinical and morphological classification of Lieberman E. B., et al. are chosen as the main ones. In this regard, such variants of disease course as fulminant and subacute myocarditis are highlighted, but omitted is acute, which occurs much more often than fulminant and requires a special algorithm for decision-making. Such rare variants of myocarditis as gigantocellular and eosinophilic remained outside the classification tables, which cannot be diagnosed without EMB, although all of them, as a rule, have fulminant or acute course. Not only granulomatous myocarditis was lost in the classification, but also the most frequent morphological variant — lymphocytic myocarditis. According to the proposed classifications, the Russian recommendations divide chronic myocarditis into active and persistent, although it is not always possible to draw a parallel between the disease course and the morphological picture. In addition, myocarditis staging and, hence, diagnosis of chronic myocarditis is performed on the basis of detection of fibrous changes in myocardium at histological examination of EMB.

Prospects of using magnetic resonance imaging (MRI) of heart for differential diagnosis of chronic myocarditis are very doubtful, as sensitivity of Lake Louise criteria does not exceed 63% [7]. And only introduction of modern methods of T2-mapping, according to experts, allows to increase sensitivity of magnetic resonance criteria for detection of active inflammatory process up to 89% [8]. From the point of view of a practical physician, the domestic classification proposed and subsequently modified by N. R. Paleev and F. N. Paleev [9] is the closest to the optimal structure (etiology, pathogenesis, morphology, prevalence, nature of course, severity and variants of debut), but needs additional correction taking into account the results of modern clinical and morphological studies. Only this type of classification will allow a decision-making strategy to be developed regarding the choice of optimal therapy. As a result, the participants of the discussion agreed that for the next document revision, it is necessary to create a unified version of the classification, devoid of above-mentioned drawbacks, which will allow to avoid the wish of doctors "*to use any version of the classification*".

In the same section of the recommendations, one of the most fundamental issues is briefly discussed — indications for EMB in patients with suspected myocarditis. This question was discussed extensively when working on the text and essentially sounds like this: Does a doctor have the right to diagnose myocarditis and prescribe its treatment when a myocardial biopsy is not possible? European experts say no. The text of the national recommendations favors the more lenient American approach, which involves dividing the indications for EMB into absolute and other indications.

Absolute indications include hemodynamic instability in patients "*with a heart failure clinic of less than 2 weeks with normal or dilated left ventricle and first-onset heart failure lasting from 2 weeks to 3 months with dilated left ventricle, recurrent ventricular arrhythmias, grade II, III atrioventricular block (atrioventricular block) or lack of response to ongoing recommended therapy for 1-2 weeks*". Obviously, these indications cover a significant proportion of patients with fulminant and acute myocarditis of moderate to severe course.

The following section on "diagnosis" lists in more detail the clinical scenarios for EMB, taken from the 2007 guidelines [10]. The first four are mainly related to myocarditis — heart failure (HF) and/or dangerous rhythm and conduction disturbances of various prescription without a sufficient response to the optimal recommended therapy. However, given the cardiotoxic effects of antitumor drugs to exclude myocarditis in patients with a history of anthracycline therapy, and subsequently in patients receiving targeted or immune therapy for cancer, EMB may also be relevant.

In the course of discussion, it was suggested that EMB is insufficiently informative and has low sensitivity and specificity. In such cases, the question always arises — what is the diagnostic significance of EMB compared to, if it remains the "gold standard" in the diagnosis of myocarditis? We can only talk about the percentage of biopsies that allowed us to make (clarify) the clinical diagnosis and determine indications for treatment. But this percentage depends entirely on the principles of selection for biopsy and the capabilities (experience) of the center. In expert centers with extensive experience in EMB, its usefulness in making a diagnosis exceeds 90-95%. The question is not about the possibility of EMB performance (many centers have experience in such manipulations), but about the prospects for further immunohistochemical and molecular genetic analysis of biopsy material. To this end, it makes sense to create a network of expertise centers in which such research can be conducted.

The second no less important question is what does EMB offer in comparison to noninvasive diagnostic methods, which are generally more accessible to Russian doctors? The recommendations provide a very detailed review of the value of the individual history (primarily the association of symptoms with past infection) and the capabilities of currently available noninvasive methods for diagnosing myocarditis. It should be emphasized that none of them has an absolute value (although all methods were evaluated for their diagnostic significance in comparison with the "gold standard" — biopsy).

Insufficient specificity of radionuclide methods (except for diagnosis of cardiac sarcoidosis), low informative value of serological and molecular genetic studies in blood serum to confirm viral etiology of myocarditis were noted. It is emphasized that an increased level of cardio-specific autoantibodies serves as an additional indication of the autoimmune nature of the pathological process. At the same time, attention should be drawn to the lack of standardized kits for the evaluation of cardio-specific autoantibodies in the Russian Federation. The place of coronarography in the differential diagnosis of myocardial damage in patients with intermediate and high pretest probability is outlined. The issue of including computed coronary angiography in the algorithm of examination of a patient with suspected myocarditis remains open, because even in case of the disease onset as an acute coronary syndrome in a patient without traditional risk factors in some cases it is more justified to perform invasive coronarography to verify the diagnosis. During the discussion of clinical manifestations of myocarditis, it was suggested to create an algorithm describing the sequence and scope of diagnostic methods, quantitative (point) criteria for making a probable diagnosis of myocarditis, but such an algorithm was not included in the final recommendations.

The significance of biomarker determination in the diagnosis and monitoring of patients with myocarditis was unexpectedly discussed. This is probably due to the wider familiarity of these laboratory indicators and the experts' greater experience in their application. However, for myocarditis, there have been no randomized studies assessing the informative value of biomarkers, so all the provisions reflected in the text of the recommendations are only extrapolations from other areas of cardiology. In particular, the appropriateness of frequent determination of NT-proBNP level was questioned by experts. In the final text of the recommendations, this study is suggested for all patients with suspected myocarditis (as an objective tool to monitor the degree of decompensation over time), but it is clear that this biomarker is nonspecific and its increase cannot be directly used to diagnose myocarditis.

The most common alternative to EMB is contrast-enhanced cardiac MRI. Suffice it to say that even the European myocarditis registry included patients on the basis of either biopsy or MRI data (the experts really assessed the situation with biopsies in European countries) [11]. The Russian recommendations quite rightly note that while MRI has a high resolution and is useful in assessing myocardial disease, "*the method sensitivity decreases in patients with a long disease course and chronic myocarditis, especially out of exacerbation. Delayed contrast <...> does not allow to differentiate between acute and chronic phases of inflammation,*

i.e. the interpretation largely depends on clinical state of the patient". It should be noted that in patients with unstable hemodynamics who are on inotropic or circulatory support, MRI examination can be performed only after hemodynamics stabilization, i.e. when they are discharged from the hospital. Therefore, in order to exclude rare variants of myocarditis, for which the prescription of combined immunosuppressive therapy is recommended, the strategy of EMB is justified. In patients with acute myocarditis with the type of acute coronary syndrome or with the picture of recent HF but preserving hemodynamic stability, cardiac MRI can be diagnosed with diagnostic accuracy of ~85% [7]. However, it should be remembered that cardiac MRI has low diagnostic value for differential diagnosis between chronic myocarditis and DCM.

Analysis of current practice in various regions of Russia with regard to myocarditis treatment shows that none of the noninvasive methods of diagnosing the disease, including cardiac MRI, usually gives the physician enough confidence to initiate specific therapy for myocarditis. There are three reasons for this: the mandatory biopsy to determine the scope and nature of drug therapy according to European experts, the insufficient evidence base regarding the effectiveness of immunosuppressive therapy, and the high risk of its side effects.

One of the main objectives of the Russian recommendations was to offer practitioners a simple algorithm for selecting a treatment for each individual case. During the discussion of treatment issues, a broad discussion unfolded. The difficulty in developing a therapeutic strategy was the fact that data from multicenter randomized trials, which have become indispensable in cardiology, are almost completely absent today. Therefore, the Russian recommendations, like their European predecessor in 2013, take into account only the opinion of experts who relied on a small number of single-center studies and data from the registry analysis.

The final recommendations included the following statement: "*Administration of glucocorticosteroids (H02AB) is not indicated in patients with acute myocarditis, with the exception of autoimmune, eosinophilic, granulomatous and giantcellular myocarditis*". It is important to note that this conclusion should equally apply to clinical cases of fulminant myocarditis. Unfortunately, when discussing the effectiveness of glucocorticosteroids in patients with acute myocarditis and unstable hemodynamics (p. 58), reference is made to the results of a single-center clinical trial of TIMIC, although the criteria for inclusion in the study refer to patients with a chronic HF clinic >6 months who do not respond to standard HF therapy, i.e. patients with chronic myocarditis or inflammatory cardiomyopathy, as this nosological form is commonly called in the English literature.

In patients with fulminant and acute myocarditis, the prevailing view is that immunosuppressive therapy is indicated only after histological confirmation that the clinical case belongs to rare variants of myocarditis (autoimmune, eosinophilic, granulomatous and giant cell). The recommendations for steroid therapy in viral-negative myocarditis also refer mainly to patients with chronic lymphocytic myocarditis, although the Russian recommendations also include rare myocarditis variants in this group. However, the evidence base for the efficacy of immunosuppressive therapy in acute myocarditis is insufficient.

The role of parvovirus infection in the development of myocarditis should be considered separately. Given the high prevalence of this viral infection in the general population and the frequent detection of the viral genome in myocardium in patients without inflammatory myocardial damage, there is an opinion that parvovirus B19 is present in myocardium in most cases as a non-specific myocarditis witness rather than as the main pathogen causing the disease [12]. Only the presence of a high titer of viral copies (>500 viral DNA copies per microgram of cardiac DNA) and confirmation of its replication are currently recognized as associated with the myocarditis development. Most of the EMB samples obtained from patients with acute or chronic myocarditis have a low abundance.

A number of studies have confirmed the efficacy of immunosuppressive therapy in patients with persistent parvovirus infection, regardless of abundance, as well as comparable efficacy of therapy in patients with myocarditis confirmed by biopsy and diagnosed without biopsy (among which there could be parvovirus-positive patients) [13, 14]. The situation is somewhat different with Ebstein-Barr virus and herpes virus type 6, reactivation of which is associated with a severe course of myocarditis. It has been shown that the genome of herpes virus type 6 can integrate into the DNA of somatic or embryonic cells. However, whether integrated viral particles can reactivate and induce myocarditis is still unclear.

During the on-line discussion, quite fair thoughts were expressed that the reasons for a strict ban on the use of steroids in severe forms of acute and fulminant myocarditis and the inability to immediately perform EMB are not enough — such an official ban would tie doctors' hands and deprive many patients of a chance for a more favorable disease course. However, it should be remembered that unjustifiably early prescription of steroids without verification of the diagnosis and using the reserve possibilities of additional (inotropic/

circulatory support) methods of treatment of acute HF may be associated with a high risk of septic complications development. Therefore, recommending telemedicine counseling and/or transferring such patients to specialized level 3 centers is important to indicate as an important step in medical care.

Regarding patients with chronic myocarditis, the recommendations on the use of immunosuppressive therapy agree with the opinion of most foreign experts: "*Immunosuppressive therapy may be considered in patients with moderate or severe heart failure, life-threatening rhythm and/or conduction disturbances with ineffective standard therapy only if histological and immunohistochemical confirmation of myocardial inflammatory disease and the absence of the viral genome in myocardial biopsy specimens are present*". To justify the alternative approach, a multicenter clinical trial is needed to confirm or refute the possibility of prescribing immunosuppressive therapy in virus-positive patients and to determine the therapy optimal dose and duration. Logically, the question was raised about the advisability of repeated myocardial biopsy to confirm the subsidence of inflammation or, conversely, in cases of ineffective treatment. However, this provision was not included in the final text of the recommendations, and the criteria for assessing the effectiveness of treatment of myocarditis and its discontinuation are not included in the document.

With regard to therapy with intravenous immunoglobulins and the use of immunosorption (selective and non-selective), the Russian recommendations are as cautious as the European recommendations issued seven years earlier (no fundamentally new studies have been added over the years): they are not recommended as mandatory treatment methods in adults. However, as noted in a recently published meta-analysis, the reason for such disappointing results was the study design and, in particular, the low representativeness of the study samples [15]. During the discussion, there were more positive statements regarding the use of plasmapheresis, therapy with intravenous immunoglobulin G (based on recent reviews), the appropriateness of using different (moderate or high) doses of immunosuppressive drugs was discussed, different regimens were proposed, but this has not yet been reflected in the document adopted.

The prescription for antiviral therapy is also not categorical: "*In real practice, where it is unlikely to obtain data on the presence of viral genome in myocardium, a consultation with infectious disease specialists will optimize the diagnostic decision and determine the advisability of initiating antiviral therapy*". But even with information about viral genome in myocardium, the choice of antiviral drugs is very limited. Recommendations reproduce the data on effectiveness of betaferon in some forms of viral myocarditis, but we have almost no own Russian experience of using this drug. And in general, the effectiveness of antiviral treatment in myocarditis is low, which is probably due not only to the lack of etiotropic drugs, but also to the complex pathogenesis of viral myocarditis (early start of autoimmune and autoinflammatory reactions). It should also be noted that in the Russian Federation, test systems originally developed for diagnosis of viral DNA by polymerase chain reaction (PCR) in serum are used for detection of viral genome in myocardium. Standardized kits to estimate the number of viral DNA copies per microgram of cardiac DNA are not currently available. In this regard, the prospects of prescribing antiviral therapy requiring at least 500 copies of viral genome in myocardium for its initiation or confirmation of viral replication by real-time reverse transcription PCR are rather dubious. The use of immunohistochemical analysis to detect VP-1 capsid protein of enterovirus in myocardium as an alternative to PCR with reverse transcription for diagnosis of enterovirus infection in myocardium in the Russian Federation does not allow to diagnose active enterovirus infection in myocardium, which also limits the use of beta interferon, proven to have a positive effect on enterovirus clearance.

Thus, the Russian recommendations are the first document regulating the management of patients with suspected myocarditis. And like any first basic document, it is not without flaws, which is primarily due to the complexity and insufficient study of the problem of inflammatory myocardial disease itself. But the accumulation of new knowledge about the etiology, pathogenesis and approaches to treatment of patients with myocarditis will allow adjustments to the presented recommendations. In particular, 2020-2021 forced us to deal with a very special form of myocarditis, coronavirus myocarditis — with prolonged persistence of the virus in the myocardium and simultaneously high immune activity, which largely determines the prognosis and requires active therapy. Note, incidentally, the provision of the national recommendations that "*vaccination against measles, rubella, mumps, influenza, poliomyelitis, and pneumococcus <...> is mandatory*". In turn, the feasibility and safety of vaccination against SARS-CoV-2 in patients with a history of myocarditis, including postvaccination myocarditis, remains an open question, which is likely to be reflected in the next revision of the recommendations.

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