https://doi.org/10.38109/2225-1685-2019-2-22-44

ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

DIAGNOSIS AND TREATMENT OF MYOCARDITIDES

DRAFT CLINICAL GUIDELINES

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Moscow, 2019

INTRODUCTION

Myocarditis means a set of clinical and morphological changes in the cardiac tissues (cardiomyocytes, cells of the conduction system, connective tissue structure, etc.) in cases where the presence of inflammatory myocardial changes of an infectious or autoimmune nature have been proven or are justifiably assumed. The inflammatory process may be both acute and chronic and is caused by the effect of different etiological factors affecting the myocardium directly and/or through allergic and immune mechanisms.

The identification of proof for inflammatory damage (clinical, histological, immunological and immunohistochemical signs), etiological damaging factors and localization of the inflammatory process are necessary and are exhibited in absolutely all patients with myocarditides.

Precise data about the epidemiology of myocarditides are unknown due to the considerable variability in the clinical manifestations. The most representative data can be obtained from autopsy materials. It is well known that myocarditis was identified in 8.6–12% of the autopsies on young patients who died from sudden heart attacks. A study of sudden death among 1.5 million US Air Force recruits showed that myocarditis was the cause of death in 5 out of 19 people, i.e., in over 25% of the cases. At the same time, this indicator was already 50% in the autopsies of HIV-infected patients. Based on the results of special studies using different diagnostic criteria of disease, the frequency of fatal myocarditis ranged from 0.15 to 0.46 for 100,000 man-years of observations. The prevalence of the severest form, giant cell myocarditis is low and is 0.0002–0.007%.

Identification of the virus genome in the myocardium does not always automatically imply the presence of myocarditis. In particular, the issue of the nature of myocardial damage (or its presence) has not yet been resolved for individuals with parvovirus B19 identified in the cardiac tissues. Thus, epidemiological data oriented only on the frequency of viral presence in the myocardium may produce distorted information and not provide an idea about the overall nature of the problem.

I. MYOCARDITIDES CLASSIFICATION

It is fairly complicated to classify myocarditides; the specialists cannot currently come to a common opinion and develop a single classification of myocarditides.

Based on the morphological pattern of the disease, according to the Dallas criteria, all myocarditides can be divided into **active myocarditides**, in which inflammatory infiltration of the myocardium is identified with necrotic or degenerative changes not characteristic for IHD, and **borderline myocarditides** characterized by a small number of inflammatory infiltrates or the absence of signs of cardiomyocyte damage.

The current international ICD-10 classification adopted in 1999 separates myocardial diseases into myocarditides and cardiomyopathies. Unfortunately, the heading "Myocarditides" only implies the acute course of the disease, while chronic myocarditides may be classified under headings I 41.0 – myocarditides in bacterial illnesses; I 41.2 – myocarditides in infectious and parasitic infections; I 41.8 - myocarditides in other illnesses classified under other headings.

N.R. Paleyev has proposed a classification that divides myocarditides by etiological factor, by pathogenesis of the pathological process, by morphology, prevalence, as well as by the clinical pattern of the disease, but from a practical viewpoint, it proved inconvenient to use.

The clinical and morphological classification initially proposed by Liberman is used most frequently throughout the world. It was further supplemented by various experts and includes six sections:

1. Fulminant myocarditis.

Fulminant myocarditis begins suddenly and has a distinct chronological interrelationship with a previous acute viral infection. About 2 weeks generally pass from the time of the viral infection and the manifestation of the disease. There is a characteristic, significant decline in cardiac contractility with relatively small dimensions of the heart. Histological study identifies numerous inflammatory infiltration foci, with possible necrotic foci as well. This type of disease can end with a full recovery, but variations of rapid progression in cardiac insufficiency and hypotension are also possible. They often result in a fatal outcome if there are no auxiliary circulatory systems.

2. Acute myocarditis.

A less rapid onset of the disease, nevertheless, it manifests this type of myocarditides also with symptoms of heart failure. This form of the disease is characterized by dilation of the cardiac cavities and diminished myocardial contractility. Biopsy samples show active or moderately active inflammatory infiltrates. Acute myocarditis generally transitions further into dilatation cardiomyopathy.

3. Chronic active myocarditis.

The onset of the disease is so blurred that the patient usually cannot speak precisely about the periods of illness. There is a characteristic moderate decline in myocardial contractility resulting in CHF of moderate severity. Pronounced fibrosis is noted in a histological study, accompanied by inflammatory infiltrative changes of a varying degree of extent. Just as in acute myocarditis, the formation of dilatation cardiomyopathy often results.

4. Chronic persistent myocarditis.

Like chronic active myocarditis, this type of myocarditis begins gradually. Histological markers are persistent inflammatory infiltrative foci with necrotic and fibrous changes. There is no significant dilation of the cardiac cavities or decrease in LV DF, which also determines the favorable outcome of the disease.

5. Giant cell myocarditis.

This type of myocarditis is characterized by the presence of giant multinuclear cells (modified macrophages within which contractile proteins, remains of phagocytized fragments of destroyed cardiomyocytes, may be detected) with signs of active inflammation, and possibly, scar tissue. The clinical pattern of this type of myocarditis shows progressive resistant cardiac insufficiency, as well as stable disorders in cardiac rhythm and conductance. The history of such patients may contain indications of various autoimmune diseases. The prognosis for this type is very unfavorable.

6. Eosinophilic myocarditis.

Eosinophilic myocarditis is yet another form. The clinical pattern of the disease, in addition to cardiac insufficiency symptoms with a slight decline in cardiac contractility, is characterized by the formation of thrombi in the cardiac cavities leading to thromboembolic complications. The history of such patients contains indications of taking some medications. The completed CBC may reveal eosinophilia. Biopsy samples, in addition to cardiomyocyte necrotic foci, may show eosinophilic dominance in the inflammatory cellular infiltrate.

Additionally, all myocarditides can be classified by the etiological factor as **infectious** and **non-infectious**.

Infectious myocarditides may include:

- Viral (enteroviruses, Coxsackie viruses, ECHO-viruses, parvovirus B-19, herpes viruses, adenoviruses, rubella, measles, hepatitis B and C, cytomegalovirus and HIV);
- bacterial (*Chlamydia, Corynebacterium diphtheria, Legionella, Mycobacterium tuberculosis, Mycoplasma, Staphylococcus, Streptococcus A, Streptoccocus pneumoniae*);
- myocarditides caused by:
  - fungi (*Actinomyces, Aspergillus, Candida, Cryptococcus*)
  - helminth invasion (*Echinococcus granulosus, Trichinella spiralis*)
  - Protozoa (*Toxoplasma gondii, Trypanosoma cruzi-Chagas' disease*)
  - Rickettsia (*Coxiella burnetti, Rickettsia typhi*)
  - spirochaeta (*Borrelia burgdorferi, Leptospira, Treponema pallidum*).

Non-infectious myocarditides include:

- myocarditides during connective tissue illnesses (systemic lupus erythematosus, dermatomyositis, polymyositis, sclerodermia, Wegener's granulomatosis and rheumatoid arthritis)
- myocarditides during systemic diseases (sarcoidosis, Kawasaki disease, Crohn's disease, non-specific ulcerous colitis and periarteritis nodosa)
- myocarditides caused by hypersensitivity to certain drugs (penicillin, sulfanilamides, tetracycline and methylodopa)

- myocarditides caused by taking cardiotoxic drugs (amphetamines, catecholamines, cocaine, streptomycin and anti-tumor drugs)
- myocarditides caused by different poisons (arsenic, iron, lead, cobalt and thallium)
- myocarditides on the background of thyrotoxicosis, courses of radiation therapy and ionizing irradiation

II. ETIOLOGY OF MYOCARDITIDES

2.1. Infectious-toxic

2.1.1. Viral

Viruses are the most frequent etiological cause of myocarditides among the European population and residents of the United States and Canada: adenoviruses and enteroviruses, including Coxsackie viruses. It was demonstrated in recent decades that myocardial infection can develop after exposure to essentially all infectious agents pathogenic for humans. Nevertheless, the frequency of identifying individual pathogens varies. Thus, in the European population in recent years, the most frequent viral genome found in myocardial biopsy samples was parvovirus B-19 and the human herpes virus 6. During these same years, in the population of indigenous Japanese, there was a sharp increase in the frequency of detection of the hepatitis C viral genome. It is important to note that in the European population, the frequency of encountering the cytomegalovirus, herpes simplex virus and Epstein-Barr virus declined, but the association of two and more viruses rose to 25%.

The frequency of myocarditis among patients infected with the immunodeficiency virus was 50% in the era before the introduction of highly effective antiviral therapy; after this group took drugs, the frequency of myocarditis development in this group declined significantly.

2.1.2 Bacterial

It has now been established that bacterial myocarditides develop considerably less often than viral. Nevertheless, essentially any bacterial agent may induce the development of the clinical pattern of myocarditis. An animal experiment proved that a combination of herpes simplex viruses with other pathogens causes more pronounced inflammatory reactions.

Various species of Chlamydia, Corynebacterium diphtheria, Haemophilus influenzae, Legionella pneumophila, Mycobacterium tuberculosis, Streptococcus A. and others have a significant impact on the frequency of development of myocarditides.

2.2. Toxic

In addition to bacterial and viral agents, myocarditides develop due to the direct toxic effect on the myocardium of drugs and the hypersensitivity reaction to drugs that results in eosinophilic myocarditis. Therapy with Aminophylline and Chloramphenicol (of the drugs used in the clinical practice of internal diseases) could result in myocarditides. Drug-induced myocarditides are characterized by a rise in the eosinophil level, combined with a pattern of myocardial damage.

2.3. Autoimmune

2.3.1. With systemic connective tissue diseases

Among the reasons for the emergence of myocarditis, a special place is occupied by myocarditides in patients suffering from systemic diseases. Developing Churg-Strauss syndrome, the oncological process of any localization, hyper-eosinophilic syndrome, helminth invasion and parasitic infections result in the development of eosinophilic myocarditis. The same eosinophilic myocarditis could develop when a tetanus vaccination is given.

2.3.2. In other conditions

The rare autoimmune myocarditides include:

- *necrotizing eosinophilic myocarditis* characterized by a high rate of increase in the symptoms of circulatory insufficiency and an extremely unfavorable prognosis;
- *idiopathic giant cell myocarditis* characterized by the presence in the myocardium of multinuclear giant cells and lymphocytic infiltration; the course of the disease is extremely unfavorable; it affects adolescents; the history of patients with diagnosed giant cell myocarditis often contains indications of intolerance for drugs;
- *cardiac sarcoidosis* (granular myocarditis without cardiomyocyte necrosis); the disease has several clearly outlined signs: it is classified as a rare disease; it is accompanied by severe conduction disorders; it is almost absolutely resistant to normal anti-inflammatory therapy.

III. PATHOGENESIS OF MYOCARDITIDES

3.1 Damaging mechanisms

The introduction of an infection into the myocardium and its development trigger the development of an inflammatory process in infection-induced myocarditides. Chronization of the process requires the presence of an intracellular infection, infection foci and altered immunity. The factors leading to enhanced susceptibility to viral infection are not completely clear.

The modern concept of the pathophysiology of viral and autoimmune myocarditis development was formed on the basis of experimental data. The primary experiments were conducted on mice using the Coxsackie virus as the infectious agent. The experiments established that the virus interacts with the cell, attaching to the endothelial receptor that was named the Coxsackie adenovirus receptor (CAR).

The Coxsackie viruses (serotypes B1 and B3, B5) use a number of factors to accelerate damage to the cellular membranes, while the adenoviruses, αV-integrins (there are currently over 20 known integrins representing a family of molecules of adhesion of the viral agent to the cardiomyocyte membrane) act as unique “co-receptors” capable of introducing the viruses into the cell.

The interaction between different factors of adhesion of the viral agent and its penetrating factors drastically raises the Coxsackie virus virulence. The expression of CAR receptors is most pronounced on cells of the brain and cardiomyocytes; the maximum receptor expression is noted in the perinatal period with subsequent age-associated drop in expression. The prominence

of CAR expression in childhood explains the high prevalence of myocarditides in the first third of life.

It has been proven in recent years that the viral invasion receptor mechanism is a universal biological mechanism (including for man as well), while the receptor blockade prevents the development of inflammation in the myocardium since it blocks the possible penetration of a virus into the cell. These data allow us to believe that at least in the acute period of the disease, most of the myocardial damage develops due to the direct viral damage to the cardiomyocytes, while the autoimmune process, characterized by generation of antibodies for cardiomyocyte membranes allows the emphasis to be shifted in the search for the most promising ways to treat myocarditides. It may be hypothesized that the receptor blockade path will be more in demand than the path of autoimmune reaction suppression, however, it should be recalled that the duration and prominence of the immune response are the determining factor for the prominence of the clinical pattern of the disease. All the patients show intensified cytokine synthesis such as the tumor necrosis factor, nitric oxide, toll-like receptors and complement. It has currently been established that all inflammation mediators play a dual role in the development of viral myocarditis:

- tumor necrosis factor – α, on the one hand, reduces the prominence of the viral load, and on the other hand, raises the prominence of the immune response and the likelihood of a fatal outcome;
- nitric oxide, on the one hand, suppresses viral replication, and on the other hand, promotes the development of the clinical manifest of cardiomyopathy, intensifying cardiomyocyte damage;
- Toll-like receptors (as well as the myeloid differentiation factor MyD88), on the one hand, minimize possible viral replication in the myocardium, and on the other hand, promote the development of inflammation in the myocardium;
- the complement not only intensifies the immune response, but also regulates the transition to dilatation cardiomyopathy.

Thus, the role of the virus introduced into the cell is obvious: replication – change in the cardiomyocyte, its death – launching of an autoimmune reaction. Study of the role of viral particles at the stage before introduction into the cell is especially important. It has been established that during this period, protease 2A (suppressing protein synthesis) is generated, which also affects the dystrophin protein that promotes cardiomyopathy development. In addition to directly affecting protein metabolism, these proteases initiate apoptosis, promoting cardiomyopathy at the same time. The role of viral proteases in myocarditides development has been established; this is the basis for the apparent new trend in pharmacological therapy for myocarditides, the development of viral protease inhibitors.

As previously noted, the altered cardiomyocytes launch immune reactions resulting in the development of inflammation in the myocardium. Analysis of the inflammatory infiltrate demonstrated that it consists of 70% mononuclears: monocytes, macrophages and T-lymphocytes. It has been established that monocytes synthesize chemo-attractant protein, while the macrophages synthesize protein 1α, which potentiates the inflammation reaction. Their blockade reduces the pronounced inflammatory reaction and the clinical manifestations of myocarditides. The T-helpers of the first and second types secrete cytokines (tumor-α necrosis factor and interleukins) resulting in the development of an inflammatory reaction. T-lymphocyte proliferation inhibition is also associated with a less pronounced inflammatory reaction. The role of CD4+T-lymphocytes in producing not only cytokines, but also antibodies for various cardiac antigens is well known. The level of such antibodies is considerably higher in patients suffering from myocarditis and DCMP. Despite treatment, the preserved high antibody level indicates the progress of the illness and its serious course.

IV. CLINICAL PATTERN AND COURSE

The first clinical manifestations of myocarditis that generally appear on the background of or within several days after the onset of an acute respiratory viral infection could be: high temperature, asthenia, rapid fatigability, and pains in various muscle groups (myalgia). Muscle symptoms are due to myositis caused by myotropic viruses (e.g., Coxsackie group A). These symptoms are the systemic manifestation of the infectious-inflammatory process and often mask the initial stage of the disease, which may occur further without any cardiac symptoms.

However, within 3-5 days after the onset of ARVI, the majority of patients begin to complain of sensations of palpitation and heartbeat interruption, dyspnea during a slight physical load and even at rest. Essentially all the patients experience dull, aching and shooting pains in the heart region, almost constant, unrelated to a physical load and not arrested by taking nitrates. The heart pains may be due to concomitant pericarditis, less often to true myocardial ischemia with its focal disease, as well as endothelial dysfunction.

The first manifestation of myocarditis may be sudden death due to ventricular tachycardia, ventricular fibrillation from myocardial focal disease localized in the area of the cardiac conducting system. Myocarditis was diagnosed in patients with idiopathic ventricular tachycardia in 33% of the cases. The disease begins fairly often with thromboembolic complications in the lesser and, less often, in the greater circulation. Severe forms of diffuse myocarditis with a rapid progression could result in acute cardiac insufficiency with a fatal outcome.

It should be noted that clinical symptoms at the initial stages of the disease in a number of cases may be missing entirely. The first subjective symptoms of myocarditis are presented in Table 1 based on the date of various authors.

The developed clinical pattern of myocarditides is primarily characterized by cardiac insufficiency. When the left ventricle is dominant in the process, the patients have symptoms of venous congestion in the lungs: moist rales, orthopnea, dyspnea and asphyxia attacks. Symptoms of right-ventricular insufficiency are manifest as a swelling in the cervical veins, hepatomegalia and peripheral edema of the lower extremities. The heart attack symptoms are generally combined with rhythm and conductance disorders, on the background of sinus tachycardia. The patients are bothered fairly often with coughing, episodes of hemoptysis due to thromboembolisms in the pulmonary artery system with the development of pulmonary infarction and peri-infarct pneumonia.

The clinical course of myocarditides depends on the involvement in the process of the left, right or both cardiac ventricles, the

nature of heart damage (focal or diffuse) and the severity of the inflammatory process. The disease may occur in a light form, including latent, and end with a full recovery. These are generally focal myocarditides. Adequate treatment of cardiac insufficiency and cardiac rhythm disorders for myocarditides of medium severity may also result in recovery within 3–6 months from the disease onset. Severe forms of myocarditides due to diffuse inflammatory damage to all heart regions occur with symptoms of progressive cardiac insufficiency, rhythm and conductance disorders, as well as thromboembolic complications. These forms frequently end in the development of dilatation cardiomyopathy or death, despite therapy.

Table 1. First subjective symptoms of disease in myocarditis patients

Subjective symptoms	
Dyspnea	68.6%
Asphyxia attacks	5.97%
Coughing	8.9%
Hemoptysis	11.9%
Palpitation	32.8%
Intermissions	16.4%
Vertigo	2.9%
Syncopal conditions	1.5%
Cardialgia	22.3%
Possible stenocardia	8.9%
Typical stenocardia	2.9%
High temperature	29.8%
Arthralgia	1.5%
High temperature + arthralgia	4.5%

The clinical course of all forms of myocarditides is also determined by the dominance of certain disease symptoms. Consequently, the following clinical versions are identified: low-symptom (latent), painful (pseudo-coronary), decompensation, arrhythmic, pseudo-valve and mixed.

V. DIAGNOSIS OF MYOCARDITIDES

5.1. Routine laboratory studies

It is not very important to conduct routine laboratory studies for myocarditides. In the CBC there might be leukocytosis and elevated ESR. During eosinophilic diseases, the number of eosinophils increases. Their activity may be determined by studying the level of eosinophilic cation protein (the significance of this test will only be established during prospective studies).

Identification of **inflammatory response markers** (C-reactive protein, fibrinogen, cytokines, etc.) could help the physician to suspect the presence of an inflammatory process in the patient; in this case, it is necessary to rule out other reasons for the rise in these parameters (acute inflammatory diseases, exacerbation of chronic conditions). Thus, peripheral inflammation markers are not specific for myocarditis and may only be viewed as an additional argument when making a diagnosis.

Necrosis biomarkers, such as cardiac troponins and creatine phosphokinase (CPK), have low specificity, but could be used to diagnose myocarditis. In patients with acute myocarditis, the concentrations of troponins I and T increase more often than the MB-fraction in CPK, while the high T troponin levels are also of prognostic importance. Troponin I has high specificity (89%), but low sensitivity (34%) for diagnosing myocarditis, while an elevated level of MB-isoenzyme of CPK is not often encountered in this group of patients.

5.2. Immunological methods of diagnosing myocarditis

The study of the cellular immune status parameters is not specific, provides limited information and cannot be used to diagnose the inflammatory process in myocarditis.

Identification of serological or molecular-genetic markers of bacterial or viral infections in the peripheral blood may not be used for the final verification of the etiological nature of the inflammatory process in myocarditis. The proof of the significance of a certain pathogen in the formation of myocarditis may be its detection in biopsy material.

An important diagnostic component is **identification of anti-myocardial antibodies** indicating the autoimmune nature of the process. In this case, the absence of an elevation in this parameter does not exclude the presence of myocarditis since the presence of an inflammatory process in myocarditis may develop without the formation of auto-antibodies detected in this test.

The immunohistochemical study with identification of specific markers such as T-lymphocytes (CD3), macrophages (CD68) and other leukocytic antigens increases the sensitivity of myocarditis identification to 50%, i.e., considerably greater than normal histological methods. An important component of etiological diagnosis of myocarditides is the identification in endomyocardial biopsy materials of infectious agents (primarily, viral) using molecular-genetic techniques.

5.3. Additional tests to determine the etiological nature of the inflammatory process

It is expedient to make additional serological or molecular-genetic studies of peripheral blood samples to establish the possible etiological nature of the process in myocarditis if the clinical pattern corresponding to this pathogen is present. It should be considered that detection of proof of a certain pathogen's presence in the body based on peripheral blood bio-samples is not strict proof of the presence of an inflammatory process in myocarditis of the relevant etiology. Serological methods should not be used as routine for a differential diagnosis of myocarditides. This may be because patients come under a physician's observation with a pronounced delay after the onset of infection (weeks-months), i.e., when the acute phase of myocarditis has already ended. In addition, the high significance of serological methods is limited by the high prominence in the population of viruses causing myocarditis. It is also difficult to interpret such results due to other factors such as reactivation or re-infection (e.g., during a herpes-virus infection), or cross reactions with the Epstein-Barr virus or enteroviruses).

5.4. Electrocardiography

Despite its low sensitivity, electrocardiography (ECG) is widely used as a screening method. ECG changes in patients with myocarditis vary from nonspecific changes in the T-wave and changes in the ST segment to infarct-like ST elevations. Disorders are also found in the atrial or ventricular behavior and different arrhythmias. We know that the presence of a pathological Q-wave or fresh blocking of the left His' bundle limb are associated with the high frequency of fatalities and the need for heart transplants.

The prognostic importance of an ECG was also studied in patients with suspected myocarditis. It was demonstrated that the clinical outcomes in the long term were associated with the following changes on the ECG registered during an EMB: duration of the QT interval with more than 440 msec, deviation in the electrical axis of the heart and ventricular extrasystole. The expansion of QRS over 120 msec was an independent predictor of cardiac death or the need for a heart transplant. Thus, an ECG is a fast and easy method for stratifying the risk of patients suspected of myocarditis.

During acute myocarditides, the ECG most often records sinus tachycardia with nonspecific changes in the ST segment and T-wave. Sometimes, a pattern is determined that is similar to a myocardial infarct with development of elevation/depression of the ST segment and the appearance of a pathological Q-wave. If there are specific disorders characteristic for pericarditis, one can suspect a combination of myocarditis and pericarditis, although this is encountered fairly rarely. An ECG has fairly low sensitivity for diagnosing myocarditis. The appearance of a pathological Q-wave and blocking of the left His' bundle limb indicate a poor prognosis and the need to start more aggressive therapy.

5.5. Echocardiography

Despite the absence of specific changes that could be identified using EchoECG, it is nevertheless expedient to conduct this study in all patients with myocarditis.

The EchoECG primarily allows the ruling out of other causes for the development of cardiac insufficiency (hypertrophic or restrictive cardiomyopathy, heart defects).

An evaluation of the dimensions of the heart chambers, thickness of its walls, as well as the primary indicators reflecting the systolic and diastolic functions of the ventricles (DF, TAPSE) helps to trace the effectiveness of the conducted therapy over time.

Patients with fulminant myocarditis often have a sharply pronounced decrease in the discharge fraction, normal dimensions of the heart chambers and thickened IVS due to myocardial edema, while patients with acute myocarditis show dilated left ventricle and normal thickness of its walls.

The presence of considerable dilation of the hear chambers with reduced overall contractility of a varying degree are more characteristic for patients with subacute and chronic myocarditis.

It is not unusual to find zones of disrupted local contractility (hypokinesia, akinesia) in patients with myocarditis, however similar changes do not permit a differential diagnosis with ischemic heart disease.

It is also necessary to conduct an EchoECG before an endomyocardial biopsy to rule out the presence of exudate in the pericardial cavity and intracavity thrombus that are determined in approximately 25% of the patients.

5.6. Magneto-resonance imaging

Magneto-resonance imaging (MRI) of the heart is currently the most informative, non-invasive instrument method of diagnosing myocarditis allowing detection and evaluation in one study of both morphological and functional disorders. The MRI arsenal includes a number of impulse sequences and techniques allowing detection and evaluation of the inflammation process in its different phases. In particular, it is mandatory that T2-suspended images be used to identify myocardial edema in the acute inflammation phase. The study protocol for patients with acute myocarditis, in addition to this, must include T1-suspended images before and after contrast staining with gadolinium agents (GD-DTPA). The study is made immediately after injection of the contrast agent to assess the so-called early accumulation. A ratio between the signal intensity from the myocardium and the signal intensity from the skeletal muscles of 4 or more indicates hyperemia and edema in the acute inflammation period. Finally, it is mandatory to conduct delayed contrasting using T1-suspended gradient sequences. Delayed contrasting allows visualization of irreversible myocardial damages. Within 10 minutes after injection of the contrast, highly intensive regions reflect fibrosis and necrosis in the myocardium while a normal (healthy) myocardium is visualized as low intensive. Delayed contrasting does not allow differentiation between the acute and chronic phases of inflammation, i.e., the interpretation depends significantly on the clinical context. Comparative studies of the magneto-resonance imaging and endomyocardial biopsy data showed that the MRI is currently the most appropriate and accurate method of visualization for inflammatory myocardial diseases associated with high sensitivity and specificity.

VI. ENDOMYOCARDIAL BIOPSY

Cardiac muscle biopsy began to be used in the 1950s, however it was limited to thoracotomy or thoracic needle biopsy with a large number (over 10%) of complications, including pneumothorax, cardiac tamponade and damage to the coronary arteries. In 1962, Sakikibara and Konno developed a catheter, transvascular technique of collecting biopsy material, after which the method became considerably safer: a special device with forceps-biotome is inserted through a guide catheter (7-8 F) set in the ventricular cavity, the biopsy forceps are brought to the ventricular wall, opened, and going slightly deeper into the endocardium, cut out a piece of endomyocardium approximately 1 x 0.5 mm. On the average, 3-6 samples are taken, preferably from different sites: for the right ventricle, this is the interventricular septum as the thickest wall of the heart chamber, for the left ventricle, selection of the biopsy site is not particularly important (most often the posterior-basal wall and apex). The biopsy samples are then sent to the pathomorphologists for light and electron microscopy. The following vascular accesses are used: for right ventricular biopsy – jugular, subclavian and femoral veins, for the left ventricular biopsy – femoral artery. Contact with the myocardium is confirmed by the sensation of stopping into the ventricular wall and by extra systoles on the ECG monitor screen. The catheter-biotome system should be checked carefully (especially during a biopsy from the left ventricle) for air bubbles and thrombi, therefore the guide catheter is constantly flushed with a heparinized physiological

solution. The procedure is conducted in an x-ray operating room under control of an ECG, fluoroscopy and pressure recording from the catheter tip (this allows certification by the pressure curve that the guide catheter is in the ventricle).

6.1. Complications of endomyocardial biopsy

The mortality rate during an endomyocardial biopsy in major clinics is under 0.05%. The main complication is perforation of the heart (0.3–0.5%), which rapidly leads to cardiac tamponade and circulatory collapse. This risk can be minimized by careful positioning of the catheter, monitoring its tip pressure and ECG. Other complications are embolization, transient arrhythmias and blockages of His' bundle limbs. These complications occur most often during left ventricular biopsy. Measures for combatting embolization are sufficient heparinization; on the other hand, in case of heart perforation, it may cause damage. It should be noted that with perforation, surgical assistance (suturing the defect) is only necessary in half of the cases, more often, conservative therapy or pericardiocentesis with return of the blood from the pericardium to the central blood channel is sufficient. A biopsy from the left ventricle must not be performed in individuals with blockage of the right His' bundle limb due to the potential of the blockage in the left limb joining with complete atrioventricular block. A biopsy should be avoided for patients with disrupted blood coagulation and previously known thrombus in the left ventricle.

6.2. Indications for performing an endomyocardial biopsy

The EMB is currently the "gold standard" in myocarditis diagnosis. However, considering the possible complications (primarily, hemotamponade, severe disorders in cardiac rhythm and conductance, thromboembolism), its use is indicated only in those cases where the EMB results may affect the patient's treatment.

Thus, EMB **should** be performed in the following clinical situations:

1. Cardiac insufficiency lasting less than 2 weeks with normal or dilated LV and disrupted hemodynamics.
2. Cardiac insufficiency lasting from 2 weeks to 3 months with LV dilation and new ventricular arrhythmias, AB-blocks of 2–3 degrees or absence of a response to standard treatment for 1–2 weeks.

EMB in these cases may also reveal severe types of myocarditis like giant cell and necrotizing eosinophilic.

Performing an EMB is also **justified** with:

1. CI lasting over 3 months with LV dilation and new ventricular arrhythmias, AB-blocks of 2–3 degrees or absence of a response to standard treatment for 1–2 weeks.
2. CI associated with DCMP of any duration, with the presence of an allergic reaction and/or eosinophilia.
3. CI with suspected anthracycline cardiomyopathy.
4. CI with restrictive cardiomyopathy of unknown genesis.
5. Suspected heart tumor (with the exception of typical myxoma).
6. Cardiomyopathy of unknown genesis in children.

The use of EMB **may** also be considered in other cases:

1. Cardiac insufficiency lasting over 2 weeks with LV dilation without new ventricular arrhythmias, AB-blocks of 2–3 degrees and good response to standard treatment within 1–2 weeks.
2. CI related to heart changes like DCMP of unknown genesis to rule out infiltrative myocardial diseases.
3. Suspected arrhythmogenic RV dysplasia.
4. Ventricular arrhythmia of unknown genesis.

In other situations (e.g., to pinpoint the reason for atrial fibrillation) it is inexpedient to perform EMB since the risk of the procedure exceeds the possible benefit.

VII. TREATMENT OF MYOCARDITIDES

Despite the fact that myocarditis treatment must theoretically be aimed at eliminating its cause, the effectiveness of such specific therapy was only confirmed during a limited number of studies including patients with such inflammatory myocardial diseases as sarcoidosis and giant cell myocarditis. It should be noted that clinical studies to assess the effectiveness of cardiac insufficiency (CI) treatment in patients with myocarditis have never been conducted, consequently we have to consider the results of experimental studies on animals.

7.1. Specific therapy

For myocardidites of a definite type, the development of which is based on autoimmune processes, immunosuppressive therapy is used, e.g., in patients with giant cell myocarditis or sarcoidosis. In the case of giant cell myocarditis, the combined use of immunosuppressant (cyclosporine and corticosteroids both in combination with Azathioprine or muronomab-CDs, and without them) may improve an unfavorable prognosis on the whole by raising the survival median rate to 12 months compared to 3 months in untreated patients. In this case, a small number of patients require the use of devices for a year for mechanical support of hemodynamics. Stopping the use of immunosuppressants could result in the development of a relapse in giant cell myocarditis, and in some cases, in the development of a fatal outcome.

For cardiac sarcoidosis, the use of immunosuppressive therapy, including high corticosteroid doses, is accompanied by an improvement in heart functioning. There is a large variability in the data with a range of 5-year survival rate from 60 to 90%. A specific therapy for viral myocardidites has not yet been developed.

7.2. Special features of treating cardiac insufficiency in patients with myocarditis.

Considering that there is no specific treatment for viral myocardidites, for which there were data on improved survival rate without the development of cardiac insufficiency (CI), therapy is currently considered symptomatic and its selection is based on the clinical manifestations of the disease. The initial drug therapy must meet modern recommendations for treating CI patients. The standard therapy for CI patients that includes the use of β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) must be started and chosen depending on the functional condition of the patient based on the results of assessing the functional class by the NYHA (New York Heart Association) classification.

7.3. Special features of using individual drug groups.

7.3.1. ACE and ARB inhibitors

Thanks to the early use of drugs blocking the renin-angiotensin system, it is possible to reduce the extent of disadaptive remodeling of the heart, and also lower the likelihood of the disease progressing to dilation cardiomyopathy (DCMP). In the experimental models of autoimmune or viral myocarditis on mice, the use of the ACE inhibitor Captopril, as well as Losartan and Olmesartan for ARB led to a statistically significant reduction in the extent of inflammation, necrosis and fibrosis. In rats with DCMP from experimental autoimmune myocarditis, Olmesartan therapy improved the left ventricular (LV) functioning and reduced the progression of cardiac remodeling. Additionally, the data obtained during the experimental studies on animals allow the hypothesis that the use of ACE and ARB inhibitors permits a reduction in the regulation of possible autoimmune components of the disease in the absence of an increased concentration of infectious agents by means of which the start of myocarditis development is possible.

7.3.2. Diuretics

Diuretics are used to prevent fluid overload. There are data that the use of Torasemide in an experimental model in rats slows down the progression of myocarditis to DCMP by reducing the prominence of fibrosis, the size of the myocytes and the myocardial protein level, transforming the β1 growth factor, as well as the levels of collagen type III and aldosterone synthase, which are not linked to the effect of the drug on the kidneys.

7.3.3. β-blockers

The use of β-blockers should not be used in the acute dissemination phase of CI even in the very early period of treating patients with fulminant myocarditis. We know that therapy with β-blockers improves functioning of the cardiac ventricle, reduces the frequency of hospitalizations because of exacerbation of SI and also increases the survival rate. The experimental study results allow the hypothesis that selection of a certain type of β-blocker affects the therapy effectiveness during inflammatory cardiomyopathy. Results were obtained that the use of Carvedilol has a noticeable effect on the heart of rats with autoimmune myocarditis by suppressing inflammatory cytokines, as well as implementing antioxidant properties, while the use of Metoprolol and Propranolol did not lead to side effects. Moreover, with the use of Metoprolol compared to a placebo in mice with experimental myocarditis caused by Coxsackie B3, there was a statistically significant increase in the prominence of inflammation and necrosis, as well as a higher mortality rate among the animals. It should be noted that the mechanism was not established that could explain such results. In patients with hypothetical myocarditis, data were obtained that allow the hypothesis that if β-blockers are not used the prognosis is poor.

7.3.4. Antagonists of mineralocorticoid receptors

The use of antagonists of mineralocorticoid receptors is recommended for patients with systolic LV dysfunction and persistent SI, the severity of which corresponds to functional class II-IV by the NYHA classification. It was established that the addition of aldosterone antagonists to standard SI therapy in such patients results in the lower need for hospitalization and improved survival rate. In mice with experimental viral myocarditis, the anti-inflammatory effects of using Eplerenone were confirmed. These effects included suppressed proteinase released by mast cells that reduced the prominence of heart remodeling by suppressing fibrosis formation.

7.3.5. Attitude towards using cardiac glycosides

It is common knowledge that the use of cardiac glycosides for patients with CI LV systolic dysfunction corresponding to functional class II-IV by the NYHA classification results in a lower frequency of complications. It should be recalled that the use of high doses of Digoxin results in the formation of pro-inflammatory cytokines and intensified prominence of myocardial damage in mice infected by the virus. In addition, taking Digoxin may limit the use of the maximum dose of the β-blocker due to the development of bradycardia or atrioventricular blocks. Consequently, the use of Digoxin should be avoided for patients with acutely developing CI that is due to viral myocarditis.

7.3.6. Calcium antagonists

On the whole, it is not recommended that calcium antagonists be used to treat patients with acutely developing CI. However, it should be noted that in the experimental model of CI induced by viral myocarditis, data were obtained that permit the hypothesis that the use of Amlodipine has a protective effect against myocardial damage in mice by suppressing the excessive formation of nitric oxide. In rats with CI induced by autoimmune myocarditis, the effectiveness of using Pranidipine compared to Amlodipine was studied. The study results indicated that both with the use of Pranidipine and Amlodipine there was a noticeable decrease in the progression of LV dysfunction and heart remodeling.

7.3.7. Opinion on the justified use of non-steroidal anti-inflammatory drugs and colchicine.

Non-steroidal anti- inflammatory drugs (NSAIDs) and colchicine are used as anti-inflammatory drugs to treat pericarditis as "non-specific" anti-inflammatory therapy, but there are no indications for the use of such drugs to treat patients with myocarditis. In the experimental models of acute myocarditis in mice, the use of Indometacin and other NSAIDs increased the prominence of inflammation in the myocardium and higher mortality rate of the animals. Consequently, the use of NSAIDs in the minimum necessary doses may be considered only when treating patients with perimyocarditis who do not have LV functioning disorders and have pronounced chest pains due to pericarditis.

7.4. Physical activity in patients with myocarditis

Aerobic physical activity must be unequivocally avoided during acute myocarditis. In the experimental model of myocarditis induced by Coxsackie virus B3, continuous physical activity was accompanied by a higher mortality rate and led to suppression of the T-lymphocyte functioning.

It should be recalled that undiagnosed myocarditis often is the cause of death among young athletes. In 2005, the relevant recommendations reflected the opinion by the experts that athletes with possible or defined myocarditis must be excluded from all sports competitions for no less than 6 months, and they can resume participation in sports competitions only if the normal functioning and dimensions of the LV have been restored with no clinically significant arrhythmias. The duration of the period during which

patients with acute myocarditis should refrain from participating in competitions after recovery continues to remain the subject of discussion. At the same time, physical loads are recommended if there are stable SI symptoms after previous myocarditis.

7.5. Implanting electrocardiostimulators and defibrillators

Implanting a temporary electrocardiostimulator (ECS) is indicative in patients with acute myocarditis who develop an atrioventricular block of II or III degree with clinical manifestations. During myocarditis caused by Lyme disease, there might be a variability in the degree of disruption in atrioventricular conductance. In any case, with a persistent atrioventricular block of III degree, the frequency of development of which is low on the whole, implanting a permanent ECD is required. Chagas' disease is characterized by the development of conductance disorders, which progress all the way until a complete atrioventricular block develops; in this disease, life-threatening ventricular arrhythmias often arise. It should be recalled that the desynchronizing effect of ECS from the right ventricle must be the grounds for refusing to use such type of ECS in patients with disrupted LV functioning, and in such cases, a biventricular ECS should be implanted. Implanting a cardioverter defibrillator (CVD) in patients with myocarditis is indicative after stopping circulation due to fibrillation of the ventricles or in the case of ventricular tachycardia with clinical manifestations. Implanting a device for resynchronizing therapy with functioning of a defibrillator is indicative for patients with CI corresponding to the II-IV functional class by the NYHA classification with disrupted LV functioning (with LV discharge fraction 35% and less) combined with blocking the left limb of His' bundle. Premature implanting the ECS or devices for resynchronizing therapy with ECS function should be avoided in patients with inflammatory cardiomyopathy, since the LV functioning may improve significantly if SI therapy is used based on current clinical recommendations. Considering the altogether less favorable prognosis, early ECS or CVD implanting may be considered in patients with sarcoidosis or giant cell myocarditis if they develop a damaged atrioventricular block of II or III degree, or ventricular arrhythmias.

7.6. Indications for using devices for mechanical support of hemodynamics and heart transplant.

If cardiogenic shock develops due to acute fulminant myocarditis, despite the use of the optimal drug therapy, the use of devices for mechanical support of hemodynamics or in vitro membrane oxygenation may be required as a temporary intervention to heal the patient or perform a heart transplant. Despite the initial severity of the condition, the prognosis for such patients is fairly favorable: the survival rate exceeds 60-80% with a high frequency of restoration of the cardiac ventricle functioning. The use of active therapy with devices for mechanical support of hemodynamics is extremely desirable and the use of such treatment approaches should be considered in the early stages for patients with acute fulminant myocarditis if full drug therapy is ineffectual.

7.7. Experimental treatment approaches

Considering the lack of proof for the effectiveness of treating patients with myocarditis that affects the pathophysiological links of the disease, different treatment approaches have continued to be studied in recent years during clinical trials. There are reports about the results of over 20 clinical trials that used immunosuppressive, immunomodulating or anti-inflammatory drugs, as well as immune-absorption therapy.

7.7.1. Immunosuppressive therapy

The efficacy of using immunosuppressive therapy was assessed during several relatively large studies and a large number of small ones. However, the results of such trials were not the grounds for using the therapy investigated in such trials as the standard for treating patients with inflammatory cardiomyopathy.

During one of the major randomized trials to assess the efficacy of immunosuppressive therapy (Myocarditis Treatment Trial), the hypothesis regarding the advantage of adding immunosuppressive therapy to the standard treatment was not successfully confirmed. No differences were noted either in the mortality rate nor the degree of improvement in functioning, LV discharge fraction within 1 year of therapy with Prednisolone combined with Azathioprine or Cyclosporine compared to a placebo. Such results could be due to the lack of a concerted opinion about interpreting the endomyocardial biopsy (EMB) results. It should be noted that during this trial, immunohistochemical methods were not used to determine the inflammation cells, and when heart tissue samples obtained from EMB were analyzed, molecular methods were not used to identify the infectious agents. Consequently, the patients whose hearts had a viral infection could obtain immunosuppressive drugs, which could result in increased viral reproduction and myocardial damage.

The majority of trials to assess the efficacy of treating patients with myocarditis for a histological assessment of the samples obtained during EMB used the Dallas myocarditis criteria. It should be noted that disputes continue even now about the applicability of using such criteria to diagnose myocardial inflammatory diseases due to the great variability in interpreting the histological study results of biopsy samples, and the impossibility of determining signs of inflammation resulting from the effect of non-cellular factors. It should be noted that the preliminary results from the ESETCID (European Study of Epidemiology and Treatment of Inflammatory Heart Disease) indicate that if immunosuppressive drugs are used, signs of myocardial inflammation cease to be determined in 59% of the patients, but such signs disappear by themselves in 40% of the patients who took the placebo. Unfortunately, the high frequency of spontaneous improvement in patients with acutely developing inflammatory cardiomyopathy was not taken into consideration in many of the trials. In order to establish the true, although moderate, effects of therapy, it is necessary to conduct new placebo-controlled trials during which such a limitation as the possible assessment of the real effect of anti-inflammatory therapy will be diminished.

It should be noted that the experts believe that the substantiation for the results of all the trials conducted as of today is limited, primarily because the majority of such trials did not use effective immunohistological and molecular methods of biological analysis of the tissue samples taken during EMB. Additionally, there was no control group in some of the trials.

7.7.2. Use of immunoglobulin

The suggestion of the possible use of immunoglobulins to treat viral myocarditis is based on data regarding their antiviral and immunomodulating effects. However, the study results

indicate that during recently developing myocarditis or dilatation cardiomyopathy, internal injection of immunoglobulin compared to a placebo did not result in additional LV functioning improvement. At the same time, the use of such therapy in children with acute myocarditis was accompanied by an improved LV functioning and higher survival rate during the first year after treatment. It should be noted that the last trial was not randomized.

7.7.3. Use of the immunoadsorption method

The use of immunoadsorption is aimed at removing anticardiac antibodies to different cardiac cell proteins that are identified in DCMP and myocarditis patients. There are data that removal of circulating antibodies using immunoadsorption improves the LV functioning in DCMP patients, diminishes the clinical and humoral markers for CI severity (endurance of physical loads, concentration of N-terminal precursor of cerebral sodium-diuretic peptide), and also improves hemodynamic indicators (increase in per-minute and per-beat heart volume, decrease in peripheral vascular resistance). Moreover, the use of immunoadsorption decreased the extent of inflammation. Immunoadsorption of protein A in patients with inflammatory cardiomyopathy improved the LV systolic functioning. Results should soon be obtained from a multicenter randomized double-blind prospective trial to assess the effects of immunoadsorption on cardiac functioning in 200 patients with DCMP. These results will apparently refine the role of this method in treating myocarditis patients.

7.7.4. Possible role of immunosuppressive therapy

The results from using immunosuppressive drugs (Cyclosporine, Prednisolone and Azathioprine) in patients with acute myocarditis were contradictory. The patients with chronic DCMP who took Azathioprine and Prednisolone showed an improved LV functioning and functional class by the NYHA classification.

The TIMIC trial (Immunosuppressive Therapy in Patients with Virus- Negative Inflammatory Cardiomyopathy) was the first randomized, double-blind, placebo-controlled trial during which from all the patients histological and immunohistochemical inflammation criteria were used to analyze the heart tissue samples obtained from EMB. Additionally, in order to exclude viral infection, all the heart tissue samples were evaluated using molecular biological analysis. The results of the TIMIC trial confirm the efficacy of using combined therapy of immunosuppressive Prednisolone and Azathioprine in patients with inflammatory cardiomyopathy without signs of viral genome in the myocardium. Data about the lack of a response reaction to therapy in 12% of the patients allows a hypothesis regarding the presence of unidentified viruses, or myocardial damage mechanisms insensitive to immunosuppressive therapy.

7.7.5. The role of antiviral therapy

The theoretical grounds for using antiviral drugs to treat myocarditis patients may be the data that most of myocardidites are the result of a viral infection. The experimental model of myocarditis induced by Coxsackie virus B3 in mice produced data that the use of interferon-β and interferon-α2 protects the myocytes from damage and reduces myocardial infiltration by the inflammation cells. However, it should be noted that the use of interferon-β alone resulted in elimination of the viral load on the heart. During the observation study, the use of interferon-β in patients with persistence of enteroviruses and adenoviruses in the myocardium and LV dysfunction led to elimination of the viral genome in all the patients, as well as an improvement in the LV functioning in 15 out of 22 patients. The results of a later randomized, placebo-controlled trial BICC (Betaferon in patients with chronic viral cardiomyopathy), which included 143 patients with DCMP of inflammatory nature and had a confirmed viral infection in the myocardium, indicated that the use of Betaferon (interferon-β-1-b) resulted in a statistically significant decrease in the viral load (enteroviruses) in the myocardium, but, on the whole, did not result in complete elimination of the virus (parvovirus B19) in all of the patients. During this trial, different indicators were evaluated, but an improvement was noted only in the CI functional class per the NYHA classification and the overall patients' assessment of their condition.

VIII. PROGNOSIS

The prognosis for myocardidites is variable and depends on many factors: etiology, histological and immunological characteristics, clinical pattern, and presence of complications and possible use of artificial circulation methods.

We know that myocarditis often occurs without symptoms and ends with complete recovery. A favorable prognosis is common for patients with acute or fulminant course of the disease (in the case of successful correction of hemodynamic instability). If the course is chronic, a considerable number of patients (up to 21% within 3 years) develop dilatation cardiomyopathy, and in this case, the prognosis depends on the presence of symptoms of chronic cardiac insufficiency.

If cardiac rhythm disorders occur, the prognosis often depends on the possibility of specific interventions, including implanting various devices.

The predictors of a poor prognosis include an increase in the QRS complex over 120 msec, the presence of syncopal conditions, low systolic arterial pressure, elevated pressure in the pulmonary artery and dysfunction of the right ventricle. The risk of an unfavorable outcome increases if the immunohistochemical study is positive and there are no beta-adrenoblockers in the comprehensive therapy. Identification of the viral genome and a positive response for the Dallas criteria do not affect the prognosis.

Despite aggressive therapy, almost 8% of the patients with lymphocytic and over 50% of the patients with giant cell myocarditis require heart transplants. Here, there is a sharp increase in the frequency of conductance disorders in the donor heart and higher transplant rejection reaction frequency. In lymphocytic myocarditis, the rejection risk rises 2-2.5 times; in giant cell, active myocarditis develops in the transplanted heart in almost every fourth patient. The average lifetime in giant cell myocarditis is 5.5 months from the time the first symptoms appear.

The prognosis for specific myocardidites (diphtheria, sarcoidosis, Chagas' diseases and others) depends on an early diagnosis and the start of pathogenetic therapy.

APPENDIX 1.

Integral significance of the clinical scenario for developing a therapeutic and diagnostic strategy

Considering that the empirical choice of the strategy for diagnosing and treating acute myocarditis is based on the clinical pattern, we cite the main clinical scenarios, their pathomorphological correlates, prognosis and the main treatment plans.

Clinical scenario	Duration of disease	Pathological correlations	Prognosis	Treatment
Acute myocarditis with infarct-like changes and symptoms	Several hours or days	Acute lymphocytic myocarditis, less often necrotizing eosinophilic myocarditis or giant cell myocarditis	Satisfactory for lymphocytic myocarditis	Symptomatic
Hemodynamically significant cardiac insufficiency regardless of the presence of LV dilation	Less than 2 weeks	Acute lymphocytic myocarditis, less often necrotizing eosinophilic myocarditis or giant cell myocarditis	Satisfactory for fulminant lymphocytic myocarditis with possible mechanical circulatory or inotropic support	Symptomatic
Cardiac insufficiency with LV dilation and new ventricular arrhythmias, disorders in conductance of high gradations, resistant to conducted therapy	Several weeks or months	Giant cell myocarditis, eosinophilic myocarditis, less often lymphocytic myocarditis	Poor. For giant cell myocarditis, mechanical circulatory support or heart transplant	Depends on pathohistological changes
Cardiac insufficiency with LV dilation without new ventricular arrhythmias, disorders in conductance of high gradations	Several weeks or months	Non-specific changes. Viral genome identified in 25-35% of cases. Dallas criteria met in only 10% of patients	Good, however high risk of progression and dilatation cardiomyopathy	Symptomatic. Possible effect on viral genome
Cardiac insufficiency with eosinophilia	Any duration	Eosinophilic or hypersensitive myocarditis, eosinophilic endomyocarditis	Poor	Symptomatic. Identification and elimination of provoking cause. With hypersensitive myocarditis, corticosteroids
Cardiac insufficiency with LV dilation and new ventricular arrhythmias, disorders in conductance of high gradations, resistant to conducted therapy	Over 3 months	Idiopathic granulomatous myocarditis (cardiac sarcoidosis), specific infections (e.g., Tr.cruzi, Borrelia burgdorferi)	With sarcoidosis, high risk of implanting of cardio-verter-defribillator or artificial rhythm driver	Symptomatic. With histologically confirmed sarcoidosis corticosteroids
Cardiac insufficiency with LV dilation without new ventricular arrhythmias, disorder in conductance of high gradations	Over 3 months	Non-specific changes. Viral genome identified in 25-35% of cases, signs of inflammation in 40%	Depends on CI DF, absence/ presence of viral genome or inflammation in biopsy sample	Symptomatic. Antiviral and/or immunosuppressive therapy

ICD 10 codes

I40 Acute myocarditis

I40.0 Infectious myocarditis

Septic myocarditis. Use the additional code (B95-B97y) if the infectious agent needs to be identified.

I40.1 Isolated myocarditis

I40.8 Other types of acute myocarditis

I40.9 Acute NOS myocarditis

I41 Myocarditis with diseases classified under other headings

I41.0* Myocarditis with bacterial diseases classified under other headings

Myocarditis: diphtheritic (A36.8+). Gonococcal (A54.8+). Meningococcal (A39.5+). syphilitic (A52.0+). Tuberculous (A18.8+).

I41.1* Myocarditis with viral diseases classifie3d under other headings

Influenza myocarditis (acute): virus identified (J10.8+) virus not identified (J11.8+) Parotid myocarditis (B26.8+)

I41.2* Myocarditis with other infectious and parasitic disease classified under other headings

Myocarditis with: Chagas' disease (chronic) (B57.2+), acute (B57.0+), toxoplasmosis (B58.8+)

I41.8* Myocarditis with other diseases classified under other headings

Rheumatoid myocarditis (M05.3+) Sarcoid myocarditis (D86.8+)

I51.4 NOS myocarditis

Myocardial fibrosis Myocarditis: NOS chronic (interstitial)