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Viral Myocarditis-Diagnostic and Therapeutic Challenge for Physicians

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SUMMARY

Myocarditis is defined as inflammation of the heart muscle according to clinical, immunohistological and pathological criteria. Myocarditis can manifest a wide spectrum of symptoms ranging from mild dyspnea or chest pain, and sometimes without a specific therapy it can lead to cardiogenic shock and death, too. According to the evidence, the incidence of myocarditis is 8-10 cases per 100.000 humans, and the prevalence of non-selected autopsies is 1-5 per 100 cases. The most common possible triggers for myocarditis are: coxsackie virus B3, parvovirus B19, adenovirus, and human herpesvirus 6. Viral myocarditis appears in three stages: acute viral infection, inflammatory cell infiltration, and myocardial remodeling. The initial patient evaluation includes a detailed history and a careful physical examination which should include an electrocardiogram, chest X-ray, blood studies, non-invasive imaging techniques. The diagnosis of myocarditis can only be obtained by investigations of endomyocardial biopsy, including: histology, immunohistology and molecular biology or virology. Therapy can be divided into supportive and specific therapy (immunosuppressive therapy, interferon, immunoglobulin, immune-adsorptive therapy, immune-modulation, vaccination).

Key words: **myocarditis, virus, endomyocardial biopsy, therapy**

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INTRODUCTION

Myocarditis is defined as inflammation of the heart muscle according to clinical, immunohistological and pathological criteria. Myocarditis is associated with myocardial inflammation usually caused by viruses, bacteria, parasites, drugs toxic effect, or it is the reaction of hypersensitivity to the drug, as in other diseases such as sarcoidosis (1). Inflammation of the heart muscle can also be caused by ischemia, mechanical trauma or it may appear in genetic cardiomyopathy (CMP).

Myocarditis can manifest a wide spectrum of symptoms ranging from mild dyspnea or chest pain and, sometimes, without a specific therapy, it can lead to cardiogenic shock and death. Dilatation cardiomyopathy (DCM) and chronic heart failure can be the major long-term sequels of myocarditis.

Recent developments in diagnosis and treatment of patients with suspected myocarditis include improved histological criteria and use of cardiovascular magnetic resonance (CMR) imaging. The standard Dallas pathological criteria for the diagnosis of acute myocarditis have often been criticized as restrictive and difficult to repeat. Variability was present in the interpretation, then the lack of prognostic significance and low sensitivity as well. These limitations have led to the development of alternative pathological classifications with criteria that rely on detection of specific cells - immunoperoxidase surface antigen staining detection, such as anti-CD3, anti-CD4, anti-CD20, anti-CD68. These criteria based on a immunoperoxidase staining protocol have higher sensitivity and may have greater prognostic value. Clinico-pathological criteria are, for instance, very important for distinguishing fulminant lymphocytic myocarditis from acute lymphocytic myocarditis. Based on these criteria, fulminant lymphocytic myocarditis has a rapid onset of viral prodromal period of two weeks before the onset of symptoms and hemodynamic collapse and has a generally good prognosis, compared to acute lymphocytic myocarditis which often has a rapid onset and does not lead to hemodynamic collapse but is a frequent cause of death or heart transplantation. It is also known that these two forms of myocarditis are not so common, which is good, but we must not forget that there is sometimes no positive correlation between clinical criteria for severity of the disease and histopathological criteria and prognosis (2).

Recent studies suggest that use of CMR may be useful for the diagnosis of myocarditis without any risk involved with endomyocardial biopsy. For example, it is proved that there is a correlation between inflamed muscle tissue and regional cardiac abnormal signals on CMR (3).

EPIDEMIOLOGY

The actual incidence of myocarditis is still unknown. Observational studies confirmed that the viral genome is more frequently present in patients with chronic DCM than in patients with valvular or ischaemic CMP, which supports the concept of viral myocarditis as the most common form of myocardial inflammation.

According to the evidence, the incidence of myocarditis is 8-10 cases per 100.000 humans, and that the prevalence of non-selected autopsies is 1-5 per 100 cases. One study has shown that myocarditis was the cause of sudden cardiac death in 8.6% of cases and it was identified in 9% of routine autopsies. Most studies have also shown that myocarditis is more common in younger people and men. Furthermore, myocarditis is a significant cause of sudden cardiac death, and CMP in children (4, 5).

The development of molecular biological techniques and the increased ability to diagnose viral infections have shown that in the previous studies DCM is associated with about 20 viruses. The prevalence of enteroviruses decreased during the past 20 years, while the prevalence of adenoviruses has increased since 1995; recently, parvovirus B19 has been the most frequently detected viral genome (6,7). Although the role of enterovirus in the pathogenesis of chronic myocarditis and DCM is well-defined, the question is whether the identification of parvovirus B19 in the heart muscle is accidental or not, and its role in acute myocarditis is still unclear (8).

Today, three biopsy series (Berlin, Baylor, Japan) have shown that the viral etiology has changed over time, and that demographic differences are still present. In the European study, Kuhl and associates showed that in 245 patients with DCM, parvovirus B19 (51.4%) was a dominant virus, followed by human herpesvirus and enterovirus, and that 27.3% of respondents had multiple infections. On the other hand, in North America, (Bowles et al. (624 respondents) indicated that the most common were adenoviruses, enteroviruses and parvoviruses B19. Literature review in the previous 20 years indicated that the most common possible trigger for myocarditis are: coxsackie virus B3, parvovirus B19, adenovirus, and human herpesvirus 6 (Figure 1) (9).

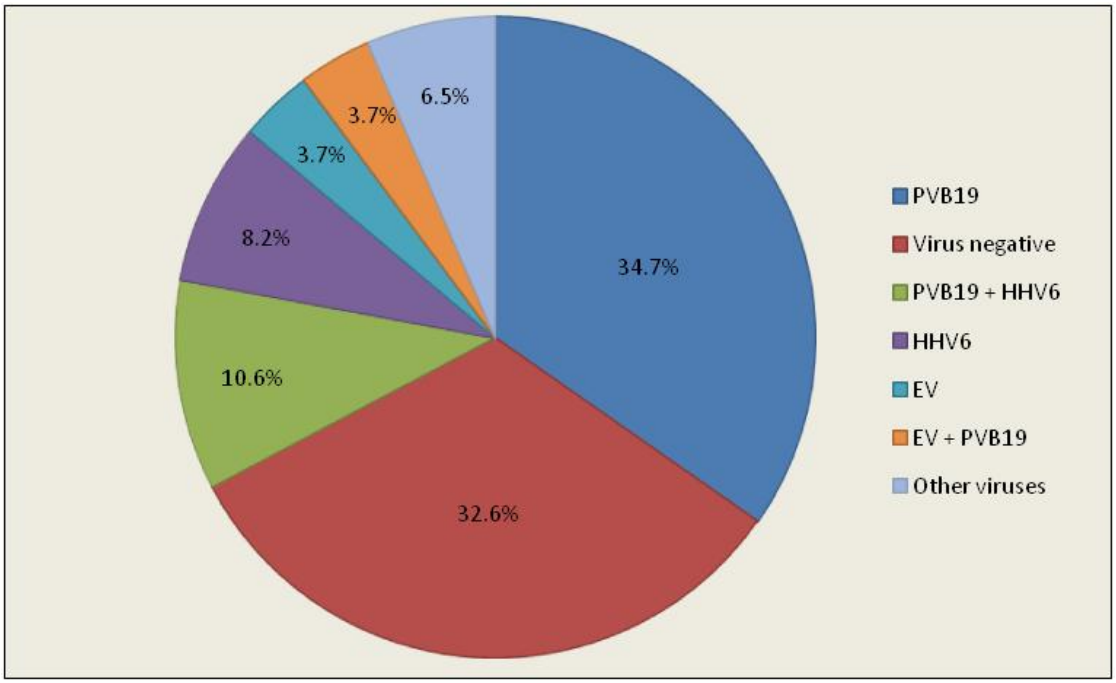

Figure 1. *Prevalence of viral genomes and multiple viral infections in the myocardium of adults (Modified from Kühll U, et al.) (9)*
(PVB19, parvovirus B19; HHV6, human herpesvirus 6; EV, enterovirus)

VIRAL CHARACTERISTICS

Adenovirus belongs to the group of DNA viruses which are responsible for mucosal infections, most commonly in children. Adenoviruses are more virulent than coxsackie virus B3 and cell necrosis is more intensive. The virus enters into the cell through the coxsackie adenoviral receptor, and infection is associated with a decrease in the number of CD2, CD3 and T cells in those where adenoviral gene is identified in heart muscle cells.

Enterovirus - Traditionally, this group of RNA viruses has been responsable for most of myocarditis cases, including coxsackie virus B3. Coxsackie adenoviral receptor is responsible for virus entry into the cell, most frequently in the cardiovascular, immune and neurological system. Enterovirus enters the host through the gastrointestinal or respiratory tract, reside in the reticuloendothelial system as an extracardiac reservoir, and attack heart tissue as a secondary target organ. A direct virus-related cytolysis of cardiomyocytes is already detected before any inflammatory infiltrate develops and appears to be decisive in fulminant cases of myocarditis.

Parvovirus - is the most common among DNA viruses. These viruses are responsible for the children's infection (fever, exanthema) and may reside asymptomatical in the bone marrow of a vast majority of the adult population. The genome of this virus is found in some studies in more than 51% of patients with DCM. These patients often complain of non-specific chest discomfort. Parvovirus B19 is found in endothelial cells and is assumed to cause endothelial dysfunction, vasoconstriction, and ventricular dysfunction (systolic and diastolic). In biopsy samples parvovirus B19 genomes have been localized in endothelial cells of venuoles, small arteries, or arterioles. Endothelial cells infection is associated with endothelial dysfunction which predicts long-term disease progression in chronic heart failure. The pathogenetic mechanisms by which B19 performs endothelial damage are complex and may involve cytotoxicity of the non-structural protein 1, transactivation of interleukin-6, and tumour necrosis factor-α, as well as induction of apoptosis.

Human herpesvirus - is a lymphotropic virus with tropism mainly for CD4+ and CD8+ T cells, B cells, and natural killer cells. It has been suggested that endothelial cells and cardiac myocytes might be an important reservoir for viral latency and reactivation. Human herpesvirus-6 becomes frequently reactivated by infections or drugs with subacute clinical manifestations, especially in acquired or drug-induced immunodeficiencies or in patients with autoimmune disorders.

Hepatitis C virus - is the most common cause of myocarditis in Asia and Japan. Symptoms are most common from first to third week of viremia, and dyspnea, palpitations and anginal pain are frequent symptoms.

Human immunodeficiency virus (HIV) - with improved survival rate in patients with HIV infection there is more information on myocarditis in these patients. In asymptomatic patients incidence is 15.9 cases with DCM per 1.000. It is difficult to make a deci-

sion about what caused myocarditis: is that HIV infection itself, immunological dysregulation, antiviral therapy, opportunistic infections, or all comorbidities.

Influenza Virus - during infection 5-10% of patients complain on cardiac symptoms. Symptoms appear on the fourth day to two weeks from the beginning of the infection. It has been reported that the pathological findings of influenza A virus myocarditis are milder than those of patients with coxsackie virus B3 myocarditis, but the clinical symptoms are relatively severe in some cases. Influenza A virus associated with fulminant myocarditis is exceedingly rare, however, there are some reported cases of fulminant myocarditis in association with pandemic influenza A virus (H1N1 typ) infection. The Japanese Ministry of Health reported of 100 deaths due to 2009 influenza A virus (H1N1 typ) pandemic in Japan; a direct cause of 6 deaths was myocarditis (10).

Mixed viral infection - it is estimated that one type of virus can increase the virulence of other viruses (coxsackie virus B3 and adenovirus), mainly due to a common cell receptor, and these infections are associated with worse ventricular function and prognosis.

PATHOGENESIS

Viral myocarditis appears in three stages: acute viral infection, inflammatory cell infiltration, and myocardial remodeling.

Acute viremic stage is characterized by early cardiomyocyte damage associated with prominent viral replication in the absence of significant host immune responses. The early phase of viral myocarditis is initiated by infection of cardiac myocytes, fibroblasts, or endothelial cells through receptor-mediated endocytosis. Acute myocardial injury can result from either direct virus-mediated lytic processes or are caused by the emerging antiviral immune response. In fulminant cases of myocarditis, resulting myocyte necrosis may cause a significant loss of contractile tissue, which is accompanied by rapidly developing heart failure and early death of the host (*early phase*). It seems that the virus enters the cardiomyocytes or macrophages via specific receptors and coreceptors. For example, a receptor for the coxsackie and adenoviruses 2 and 5 is the coxsackie adenoviral receptor receptor (11). Coreceptor has a role in serotypes B1, B2, and B5, and it is estimated that this activation may play a role of coreceptor acceleration and can cause an increase in virulence of coxsackie virus B3. Virulence of coxsackie virus B3 virus depends on the viral genome, as well as a host of factors, which may be increased by deficient levels of selenium or copper (12).

The second stage of infection is featured by inflammatory cell infiltration which results in further damage to the myocardium. The initial immune response is essential in defending the body during early infection. In response to viral infection, natural killer cells and macrophages cause profound cytokine production (tumour necrosis factor-α, interleukin-1, interleukin-2, and interferon gama) and inflammatory cell infiltration of the myocardium.

The third stage consists of fibrotic reparation and cardiac dilatation in the presence or absence of low-level persistent viral genomes (Figure 2) (13).

CD4+ T cells are primary cells responsible for damage of cardiomyocytes. T cells response is associated with the production of Th1 cytokines and Th2, which are important for the pathogenesis of myocarditis after viral infection. Recently, a third group of cells have been found (Th17) which produce interleukin 17, which also plays an important role in the pathogenesis of viral myocarditis. The important role of T cells in the pathogenesis of myocarditis in experimental models has led researchers to focus their research work on the anti-T cell therapy for severe forms of CMP. Cardiac cell damage, in the first phase of activation of innate immunity, may appear as a result of direct effects of the viruses themselves, cell apoptosis and activation of T cytolytic lymphocytes. In the further stage, the virus produces enzymes such as proteases A2 that break down cytoskeleton (dystrophin-sarcoglycan) and leads to myocyte remodeling and destruction. Viruses can activate the receptor-associated kinase P56, Fyn and Abl that also alter myocyte cytoskeleton and facilitate the penetration of other viruses. Production of matrix metalloproteinase leads to degradation of collagen and elastin. Important place of myocarditis pathogenesis belongs to the mechanism of molecular mimicry, which means that the activated T killer cells are not just attacking viruses and viral antigens, but they can function on their own proteins in this case of myosin. Further activation of B cells leads to production of specific antibodies as a central place in the subacute and chronic phase of myocarditis. This leads to further necrosis, fibrosis, cardiac remodeling, dilatation, and chronic heart failure.

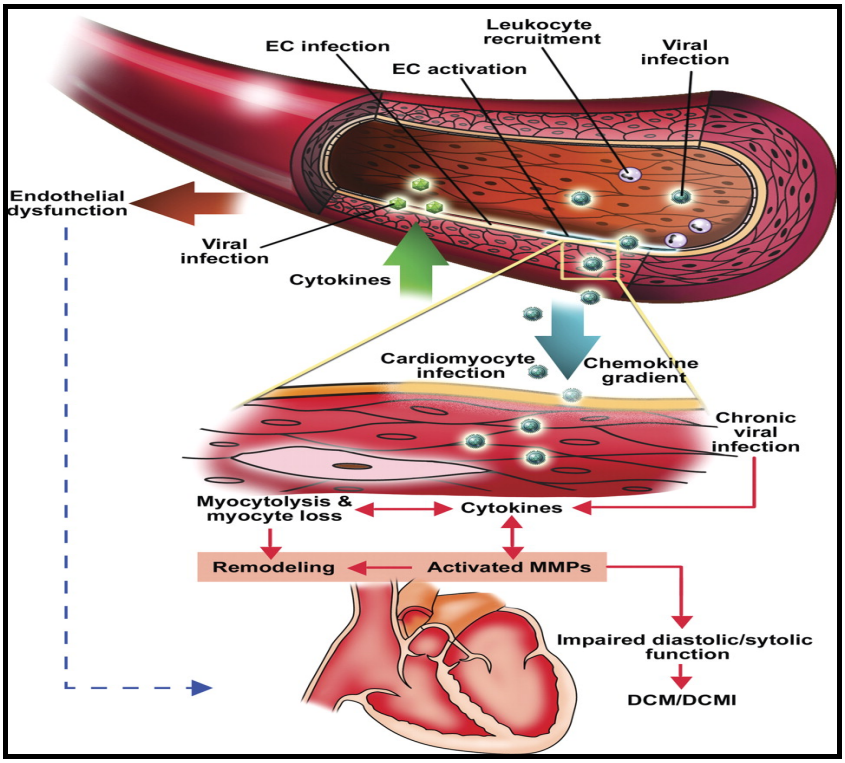

Figure 2. *Phases of myocardial injury in infection and post-infection myocarditis. (Adapted from Schultheiss HP, et al). (22)*
(EC, endothelial cell; MMPs, matrix metalloproteinases; DCMI, inflammatory DCM)

CLINICAL PRESENTATION

Acute myocarditis is often first diagnosis of non ischemic DCM in patients with symptoms that last several weeks to several months. The clinical presentation is heterogeneous, the disease manifests itself in different ways, from asymptomatic form to sudden cardiac death, sometimes with onset of ventricular arrhythmias, complete heart block, acute myocardial infarction-like syndrome. Cardiac symptoms may take the form of dyspnea, reduced exercise tolerance, palpitations, chest pain, syncope. Chest pain in acute myocarditis can be from associated pericarditis and then it is myopericarditis; more rarely, it is due to spasm of the coronary arteries (14). During the prodromal period, patients may complain of fever, mialgy, respiratory or gastrointestinal symptoms. The clinical picture in children is usually more dramatic than in adults. The physical findings often show peripheral type of cyanosis, tachycardia, cardiac dysrhythmias, third and fourth sound, heart murmurs, pericardial friction rub, mild and filiform pulse.

DIAGNOSIS

The initial evaluation of acute myocarditis includes a detailed history and a careful physical examination searching for any potential features that may provide clues to its aetiology. Additional technical examination should include an electrocardiogram, chest X-ray, blood studies, non-invasive imaging techniques, and EMB.

The electrocardiogram can show non-specific ST segment and T wave changes in the form of elevation or depression, sinoatrial, atrioventricular block, cardiac rhythm disturbances, Q wave. Ukena C. et al. have shown that prolonged QRS duration (≥120 msec) can be an independent predictor for cardiac death or heart transplantation in patients admitted to hospital with suspected myocarditis without previous heart failure. QTc prolongation over 0.440 ms, an abnormal QRS axis, and ventricular ectopic beats are also associated with clinical outcome, but do not appear to be independent predictors. These readily available electrocardiogram parameters could provide important information for managing patients with suspected myocarditis. Other electrocardiogram changes, in particular, the signs of ischaemia, seem to have no prognostic value (15).

Chest X-ray is correlated with the degree of myocardial damage and chamber dilatation.

Laboratory parameters (C-reactive protein) may indicate inflammation and elevated levels of troponin, and creatine phosphokinase isoenzyme MB (CK-MB) may indicate myocardial necrosis, although studies have rarely shown elevated markers of myocardial necrosis. The sensitivity of CK-MB for myocarditis is about 8%. Troponin T values for more than 0.1 ng/mL have a sensitivity of 34% to 53%. Other markers such as cytokines, complement, anti-viral antibodies (a four-fold

increase defines an acute infection) still are not used to confirm myocarditis. Mahfoud F. et al. showed in their study that virus serology (detection of IgM, IgA, or IgG) has no relevance for the diagnosis of myocardial infection in patients presenting with suspected myocarditis. Even in the subgroup of patients with histopathological signs of inflammation in the myocardium, a lack of correlation remains. Evidence of an acute viral infection by serological determinations was found in the serum of 20 patients (16%), of whom only 5 patients had virus genome and only 6 patients showed the evidence of inflammation in the myocardium. *Serological examinations are expensive and unreliable in clinical practice and should no longer be used as a standard means in the work-up of patients with suspected myocarditis. Endomyocardial biopsy offers the possibility for an exact diagnosis and appears to be underused* (13).

Echocardiographic findings may be of great help in the initial evaluation of patients. The parameters monitored are mainly related to left ventricle; left ventricular dilatation or hypertrophy, or regional changes in contractility. It can detect the existence of a thrombus in the cardiac cavities, pericardial effusion, and Doppler can quantify mitral and/or tricuspid regurgitation. Right ventricular dysfunction is an uncommon but important predictor of death or cardiac transplantation. Latest imaging techniques including strain echocardiography may have better sensitivity and specificity for myocarditis.

Radionuclide methods using indium - 111 antimiozin antibodies have the highest sensitivity that is in the range from 85% to 91%. This method indicates the existence of myocytes with compromised membranes integrity and is included in studies with a large number of positive biopsy in myocarditis. Unfortunately, due to its limited availability, pronounced radiation exposure, and 48 h delay in obtaining images, its use remained restricted.

Coronary angiography showed normal arteries, a heart catheterization is used mostly for endomyocardial biopsy.

CMR in suspected myocarditis can localize and quantify tissue injury, including edema, hyperemia, and fibrosis. CMR is one of the latest approaches in the diagnosis of myocarditis and is very suitable for its characteristics to define the character of the heart tissue by the contents of H_2O and contrast kinetics. In the recent series of 82 patients with myocarditis who had biopsy-proven disease, CMR alone made the correct diagnosis in 80% of cases (16). The use of contrast media such as gadolinium-diethylene triamine pentaacetic acid (gadolinium-DTPA) helps to separate accurately the healthy from inflamed or damaged tissue. It is interesting that on the basis of this finding in the studies confirmed that the lateral wall is the most affected one by inflammatory process and not the septum as it has been previously thought. The importance of CMR is the fact that it is a non-invasive method, there is no risk like during the endomyocardial biopsy, and it can be used to monitor the effects of the therapy. In biopsy studies that were conducted with CMR, positive and negative predictive values were 71% and 100% (17).

HISTOLOGICAL EVALUATION

The diagnostic gold standard is EMB with the histological Dallas criteria in conjunction with the new tools of immunohistochemistry and viral polymerase chain reaction (PCR). EMB can be performed with a very low major complication rate, when performed by highly experienced operators. The American Heart Association, the American College of Cardiology, and the European Society of Cardiology joint scientific statement recommended that EMB should be performed (class I indication) in patients with heart failure and a normal sized or dilated left ventricle, two weeks of symptoms, and hemodynamic compromise, and also in patients with a dilated ventricle, two weeks to three months of symptoms, new ventricular arrhythmias or Mobitz type II second degree or third degree heart block, or who fail to respond to usual care within one to two weeks (18). According to the Dallas criteria, findings of myocyte necrosis and inflammatory infiltrate are needed to confirm myocarditis *(acute myocarditis)*. *Borderline myocarditis* implied presence of inflammatory infiltrates but with no evidence of myocyte injury. In addition to these findings, there are also *persistent myocarditis*, *healing myocarditis* and *healed myocarditis*. It is recommended that CMR should be performed before taking the tissue samples, to reduce the sampling error.

For further analysis, immunohistochemistry has to be performed. According to the World Health Organization and the International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, EMB were considered inflamed in the case of immunohistochemical detection of focal or diffuse mononuclear infiltrates [>14 leucocytes/mm2 (CD3 + T lymphocytes and/or CD68 + macrophages)] in the myocardium, additionally to enhanced expression of human leukocyte antigen class II molecules (19).

After that, PCR is needed for molecular detection of the viral genome. A viral load of ≥500 genome equivalents per microgram in EMB specimens has been shown to be a clinically relevant threshold for the maintenance of myocardial inflammation.

CRITERIA FOR VIRAL MYOCARDITIS DIAGNOSIS

When talked about the probability of myocarditis existence, one should mention *suspected myocarditis*, a *condition compatible with myocarditis* and *myocarditis with high probability*. If there are two positive categories, myocarditis is suspected, three positive categories indi-

cate the condition compatible with myocarditis and myocarditis with a high probability is diagnosed if there are four positive categories (Table 1).

Table 1. *Criteria for diagnosis of myocarditis (Modified from Braunwald's Heart Disease 8th edition, Myocarditis) (1)*

CATEGORY 1 - Clinical Symptoms	**CATEGORY 2**
1. Clinical heart failure	1. Echocardigraphy evidence
2. Fever	2. Regional wall motion abnormalities
3. Viral prodrome	3. Cardiac dilatation
4. Fatigue	4. Regional cardiac hypertrophy
5. Dyspnea on exertion	5. Troponin release
6. Chest pain	6. High sensitivity (>0.1 ng/mL)
7. Palpitations	7. Positive indium-111 antimyosin scintigraphy and normal coronary angiography or absence of reversible ischemia by coronary distribution on perfusion scan
8. Presyncope and syncope	
CATEGORY 3 - CMR	**CATEGORY 4 - Myocardial biopsy**
1. Increased myocardial T2 signal	1. Findings compatible with Dallas criteria
2. Delayed contrast enhancement following gadolinium-DTPA infusion	2. Presence of viral genome by PCR or in situ hybridization

PROGNOSIS

Patients with acute myocarditis and minimal cardiac damage are mostly healed without any serious sequels later. In patients with more serious symptomatology, the outcome can be uncertain, and heart muscle impairment is evident. In patients with severe forms, only 1/3 will have preserved ventricular function, while in 25% there will be a need for a transplant. Therefore, it can be concluded that the prognosis depends on clinical presentation, ejection fraction less than 40% and pulmonary arterial pressure, and some of the independent clinical factors are the appearance of syncope, and bundle branch block on electrocardiogram (20). There is evidence that patients with fulminant myocarditis have better prognosis than those with acute myocarditis or non-fulminant myocarditis with giant cells. In a prospective study of Mc Carthy et al. who selected patients according to clinical presentation and biopsy it was shown that patients with fulminant myocarditis had average survival rate about 11 years, compared to 45% of those with non-fulminant myocarditis (21). Majority of patients recover completely (80%-90%) and a small number of patients get into the chronic phase of the disease with signs of heart failure and heart rhythm disorders. Rarely, the outcome is heart failure with terminal heart transplantation or death (cardiogenic shock, thromboembolic complications, malignant heart rate disorders).

THERAPY

Patients with acute myocarditis should limit physical activity, as exercise during active viral infection may increase viral replication and shorten survival. Therapy can be divided into supportive (heart failure therapy, heart rhythm disturbances, cardiogenic shock, bundle branch blocks), and specific therapy (immuno-suppressive therapy, interferon, immunoglobulin, immune-adsorptive therapy, immune-modulation, vaccination). In terminal heart failure, heart transplant should be considered. Heart failure therapy involves administration of diuretics, vasodilators, inotropa, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, anticoagulation therapy and the mechanical support with intraaortic balloon pump or ventricular assist devices in cardiogenic shock as a bridge to recovery or heart transplantation (Figure 3).

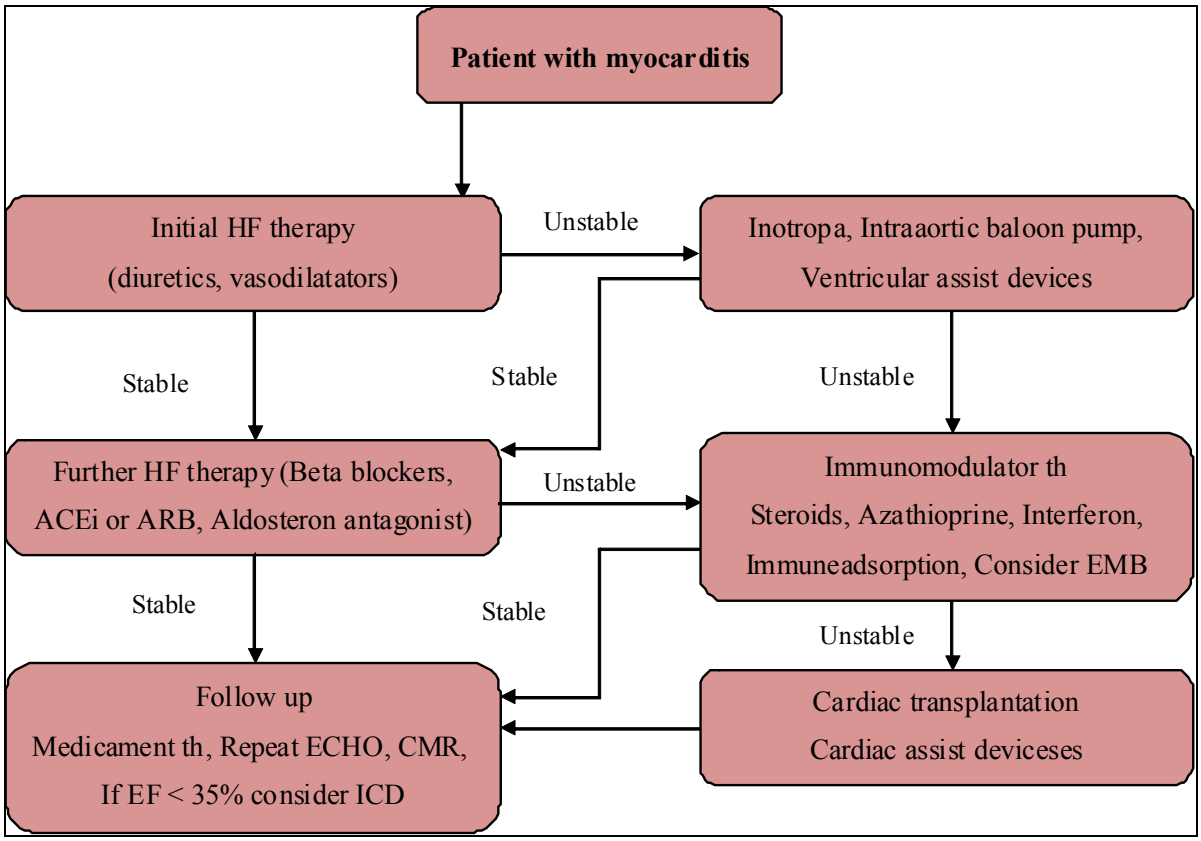

Figure 3. *Treatment algorithms for patients with myocarditis, depending on hemodynamic stability and response to general supportive and remodeling therapy. (Modified from Braunwald's Heart Disease 8th edition, Myocarditis) (1) (HF, heart failure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; EF, ejection fraction; ICD, implantable cardioverter defibrilator)*

Treatment of early disease

There are data of early disease treatment, which means the elimination of viral translation, transcription, and proliferation with the administration of antiviral medications that target viral attachment to host-cell receptors, virus entry, or virus uncoating, would be effective in the early stages, but, unfortunately, most adult patients are treated in the chronic phases of the disease. These agents, therefore, are of limited administration in virus-associated heart disease. One of them is Pleconaril that prevents the virus from exposing its RNA, and also prevents the virus from attaching itself to the host cell. The current challenge of antiviral therapy in patients with chronic cardiac viral infections is the time when to begin the treatment in order to prevent the progression of myocardial injury by viral clearance before chronically infected heart tissue is irreversibly damaged (Table 2) (22).

Table 2. *Potential pathogenesis-directed therapies depend on the phase of myocarditis (Modified from Schultheiss HP, et al) (22)*

PHASE OF DISEASE	PROPOSED MECHANISM AND INFECTIOUS AGENTS	POTENTIAL THERAPY
	Symptomatic heart failure medication	
Acute myocarditis (early phase)	Direct cytopathic injury	Antiviral agents?
	Activation of macrophages, natural killer cells, and cytokines	Antiviral agents? intravenous immune globulin?
Post-infectious (auto)immunity	Activation of T-cells, B-cells, antibody production	Steroids, Immunoadsorption Intravenous immune globulin Muronomab-CD3
Chronic viral cardiomyopathy	Enterovirus	Interferon beta
	Adenovirus	Interferon beta
	Erythro-or parvovirus	Intravenous immune globulin (acute infection) Type I interferons (chronic infection)
	Human herpesvirus 6	Ganciclovir
	Ebstein-Barr virus Cytomegalovirus	Ganciclovir Foscarnet, Cidovir
	Herpes simplexvirus, Varicella	Aciclovir
	Respiratory syntitial virus	Ribavirin
	Hepatitis C virus	Pegylated Interferon-α + ribavirin
	HIV	Anti-retrovirals

Treatment of chronic viral heart disease

Interferon beta - it was shown that beta interferon can decrease the number of viruses up to complete regression of viral particles, the accumulation of viral RNA and viral coat protein. Kuhl et al. have shown that the use of interferon beta (IFN-β1a) may affect the elimination of viruses, repair left ventricular ejection fraction and clinical status of patients. They have evaluated 22 patients with DCM and biopsy evidence of viral persistence (enterovirus and adenovirus). The drug was administered subcutaneously every other day in addition to constant heart failure medication for a period of 24 weeks. The patients entered a initial period (one week) during which they received 2×10^6 IU IFN-β, then within the following 2 weeks the study medication was elevated to 4×10^6 and 6×10^6 IU IFN-β, respectively, and continued for the following 21 weeks. The mean left ventricular ejection fraction improved from 44.6% to 53.1% ($P<0.001$). Overall, the patients also improved in clinical status. Therefore, the complete clearance of both viruses after treatment suggests that early biopsy-based diagnosis and timely treatment may prevent disease progression and thereby improve the outcome of chronic viral CMP (23).

In the study of Schmidt-Luce et al. parvovirus B19 and human herpes virus-6 responded not so well upon IFN-β treatment with respect to virus clearance and hemodynamic changes, although affected patients can improve clinically, despite incomplete virus clearance following reduction of virus load and/or improvement of endothelial dysfunction. Complete clearance of those viruses may need longer treatment intervals, higher doses, or even a complete change of the antiviral treatment regimens (24).

Currently, there is no approved treatment for chronic viral heart disease, but data from studies have demonstrated that subgroups of patients, who had not improved upon regular heart failure medication, may get significant benefit even years after the onset of chronic disease; effective treatment conditions for viru-

ses, other than enterovirus and adenovirus, have not yet been tested completely.

Immunosuppressive therapy - administration of immunosuppressives (corticosteroids, azathioprine, cyclosporine) is still controversial and the question is when to begin with this treatment because the immune response can be both useful and harmful. In published randomized study on the Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC study), the authors confirmed a positive treatment response in patients with chronic active myocarditis (25). This study included 85 patients with myocarditis and chronic (>6 months) heart failure unresponsive to conventional therapy, with no evidence of myocardial viral genomes. Patients received either prednisone 1 mg/kg per day from 1 to 4 weeks followed by 0.33 mg/kg per day for 5 months and azathioprine 2 mg/kg per day for 6 months in addition to conventional therapy for heart failure. Primary outcome was the 6-month improvement in the left-ventricular function. Group 1 (prednison or azathioprine) showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left-ventricular dimensions and volumes compared with baseline, and none of placebo groups showed improvement in ejection fraction that significantly worsened compared with baseline.

Thus, according to the studies performed until now, immunosuppressive therapy should not be routinely applied in patients with myocarditis. However, patients with giant cell myocarditis, autoimmune or hypersensitive myocarditis with heart failure can benefit from this therapy. The best responders may be those with active autoimmune response without persisting viral genome. We need to be aware that this is unlikely to influence the ultimate mortality of the patient, but it may improve the short-term natural history (1).

Immunoglobulin - acute-onset DCM, including peripartum CMP, are likely to represent an autoimmune inflammatory process in the myocardium that is triggered by a transient viral infection. Instead of anticytokine or immune-suppression therapy, a possible strategy is passive immunization through the infusion of immune globulins. In cases of pediatric heart failure, particularly myocarditis, uncontrolled studies suggested a potential benefit with intravenous immune globulins.

McNamara et al. conducted a study involving 62 patients with acute heart failure, many of whom also had concurrent myocarditis, and randomized the patients with 2 g/kg intravenous immune globulin or placebo, followed up for changes in left ventricular ejection fraction from the baseline to 6 months and 12 months (Controlled Trial of Intravenous Immune Globulin in Recent Onset Dilated Cardiomyopathy **-** IMAC II trial). The improvement of left ventricular ejection fraction was identical in both the intravenous immune globulin treatment arm and in the placebo arm. These results suggest that for patients with recent-onset of DCM, immune globulin does not augment the improvement in left ventricular ejection fraction. *There are no reliable data for the application of this type of therapy in the adult population with viral myocarditis than those who do not respond to immunosuppressive therapy* (1).

Adsorptive Immune Therapy - involves the use of plasmapheresis to remove circulating cytokines and antibodies to cardiomyocites, beta-adrenergic receptors, adenosintriphosphat carriers, myosin. If this treatment is applied five or more days, besides the elimination of circulating antibodies and immune complexes, it also effects the elimination from the heart muscle, as well. *However, this form of therapy should be confirmed in larger studies.*

Vaccination - since viruses are the most common cause of myocarditis, it is logical that the administration of vaccination could lead to a lower percentage of myocarditis development.

CONCLUSION

Myocarditis is the disease with different clinical course, difficult to diagnose. There are no clear recommendations, and therapy and prognosis are often unclear. CMR has the highest sensitivity for myocarditis, but further confirmation in chronic myocarditis is needed. When it comes to treatment, the highest expectations are focused on the administration of interferon, immunomodulatory therapy and vaccination.

Patients with myocarditis should have full attention, especially those with mild clinical symptoms and those with an acute course, because, as already mentioned, severity of the clinical presentation does not correlate with the outcome.

New researches are required in order to provide a clear diagnosis, monitoring the effects of therapy and prognosis, using new diagnostic techniques and biomarkers in patients with myocarditis.

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VIRUSNI MIOKARDITIS - DIJAGNOSTIČKI I TERAPIJSKI IZAZOV ZA LEKARE

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Sažetak

Miokarditis se definiše kao zapaljenje srčanog mišića prema kliničkim, imunohistohemijskim i patološkim kriterijumima. Miokarditis se može manifestovati širokim spektrom simptoma od blage dispneje do bola u grudima, a ponekad bez specifične terapije može dovesti do kardiogenog šoka i smrti. Prema podacima, učestalost miokarditisa je 8-10 slučajeva na 100000, a prevalenca na neselektovanim obdukcijama je 1-5 na 100 slučajeva. Najčešći mogući izazivači miokarditisa: koksaki virus B3, parvovirus B19, adenovirusi i humani herpesvirus 6. Patogeneza virusnog miokarditisa prolazi kroz tri faze: akutne virusne infekcije, infiltracije zapaljenskim ćelijama i remodelovanja miokarda. Početna evaluacija bolesnika obuhvata detaljnu istoriju bolesti i pažljiv fizički pregled; u daljem toku treba uraditi elektrokardiogram, rentgen srca i pluća, analize krvi, neinvazivne metode snimanja srca. Dijagnoza miokarditisa može se postaviti samo endomiokardnom biopsijom, uključujući: histologiju, immunohistologiju i molekularnu biologiju ili virusologiju. Terapija se može podeliti na suporativnu i specifičnu terapiju (imunosupresivna terapija, interferon, imunoglobulini, imuno adsorptivna terapija, imuno-modulacija, vakcinacija).

Ključne reči: **miokarditis, virus, endomiokardna biopsija, terapija**