Update on myocarditis – review (RCD code: III-6A.1)

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Abstract

Myocardits is an inflammatory disease of the myocardium diagnosed by established histological and immunohistochemical criteria. The true incidence of myocarditis is unknown. There are numerous potential etiologic factors, however, in developed countries the most frequent cause of myocarditis are viral infections. The pathogenesis of viral myocarditis and subsequent dilated cardiomyopathy (DCM) is not fully understood and differ between viruses. The progression of acute cardiac inflammation to DCM is the three-phase process, including viral (cytopathic), (auto)-immunulogic, and recovery or myopathic phase. Cardiac symptoms are variable and include reduced functional capacity due to dyspnoe and/or fatigue, palpitations, precordial chest pain which result from associated pericarditis or coronary artery spasms. Diagnostic work-up in myocarditis is multistage and requires integration of clinical symptoms, laboratory and imaging data, all of which have an adjunctive role to the endomyocardial biopsy (EMB), which is final and ultimately decisive diagnostic tool. All patients with clinically suspected myocarditis should undergo detailed echocardiographic examination to rule out other cardiac diseases and to assess and monitor changes in chamber size, wall thickness, ventricular systolic and diastolic function, or pericardial effusions. Nevertheless, cardiac magnetic resonance is superior to echocardiography in terms of non-invasive tissue characterization. Recent trails have provided substantial body of evidence for additional myocarditis-specific or tailored therapies, including anti-viral and immuno-modulating therapy such as high dose intravenous immunoglobulin, immunoadsorption, and immunosuppression. JRCD 2014; 1 (6): 4–9

Key words: myocarditis, endomyocardial biopsy, viruses

Introduction

Despite enormous progress in many areas of contemporary cardiology, myocarditis is still one of the few unconquered territory. Ambiguous diagnostic criteria, unspecified clinical symptoms and infrequent utilization of endomyocardial biopsy (EMB) lead to under-diagnosis and under-treatment of myocarditis. Fortunately, very recent studies provided new insights and freshness to the outdated view on myocardits.

Definition

According to the recent definition, provided by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, myocardits is an inflammatory disease of the myocardium diagnosed by established histological and immunohistochemical criteria. Histological assessment is based on the Dallas criteria that require the presence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischemic origin. Immunohistochemical criteria are precisely defined as more than 14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of more than 7 CD3$^+$ T-lymphocytes/mm^2 [1]. Therefore, in the view of the accurate diagnostic criteria, myocarditis cannot be diagnosed without EMB and state-of-the-art assessment of myocardial tissue.

Epidemiology

The true incidence of myocarditis is unknown due to occult infection in majority of patients, rare usage of EMB, or incomplete assessment of cardiac samples (lack of immunohistopathology or molecular analysis). Indirect data showed that 46% of children and 9-16% of adults with unexplained dilated cardiomyopathy (DCM) have myocardial inflammation, respectively [1]. Myocarditis, being also a substrate for sudden cardiac death (SCD), was reported in 2 to 42% of studied autopsies [1, 2].

Table 1. Etiology of mycocarditis

Infectious agents	Non-infectious agents
RNA viruses: *picorna-viruses* (***Coxackie A/B,*** echoviruses, polioviruses, **hepatitis C virus**), *orthomyxoviruses* (influenza A and B viruses), *paramxoviruses* (respiratory syncytial virus, mumps virus), *togaviruses* (rubella virus), *flaviviruses* (dengue virus, yellow fever virus), rabies virus, human immunodeficiency virus-1	**Autoimmunologic diseases:** systemic lupus erythematosus, dermatomyositis, rheumathoid arthritis, Sjogren syndrome, Wegenr granulomathosis, sclerodermia
DNA viruses: *adenoviruses* (A 1–5), *erythroviruses* (***parvovirus B19 type 1 i 2***), *herpesviruses* (***human herpes virus 6, cytomegalovirus, Epstein-Barr virus,*** varicella-zoster virus)	**Systemic diseases:** Churg-Strauss syndrome, sarcoidosis, Kawaski disease
Bacterias: ***chlamydie, borrelia burgdoferi,*** haemophilus influence, legionella, myocobacterium tuberculosis, neisseria meningitis	**Drugs:** antracyclines, cyclophosfamid, 5-fluorouracyl, transtuzumab, metylsergid, cocaine, fenytoine, zidowudine
Ricketssiae: coxiella burnetii	**Hypersensitivity reactions to drugs:** azitromycine, sodium azide (an additive in the dobutamine solution), lithium, methyldopa, mexiletine, tricyclic antidepressant, dapson
Fungi: actinomyces, aspergillus, candida, histoplasma, cryptococcus	**Hypersensitivity reactions to toxins:** bee sting venom, wasps, scorpions, snakes
Protozoa: ***trypanosoma cruzi (Chagas disease)***/brucei, toxoplasma gondi, entoameba histoloytica	
Worms: ascaris lumbricoides, echinococcus granulosus, schisostoma	

Etiology

Although there are numerous potential etiologic factors, in developed countries the most frequent cause of myocarditis are viral infections. Only those viruses with special affinity to cardiac tissue, termed cardio-tropic viruses, can produce myocardits. Interestingly, the spectrum of viruses isolated from heart changed over the last decades with Coxsackie virus type B being the most prevalent in 1990s whereas in the last years parvovirus B19 became the number one [1, 3]. Although human immunodeficiency virus (HIV) is not typically cardio-toxic, nevertheless is relatively frequent cause of myocarditis and DCM due adverse reactions of antiviral therapy and opportunistic co-infections. Apart from viruses, there are other less frequent infectious causes as well as immune-mediated and toxic-mediated myocardits (Table 1).

Pathology

The pathogenesis of viral myocarditis and sub-sequent DCM is not fully understood and differ between viruses. Entero-viruses, such as Coxsackie-virus enter through the gastrointestinal or respiratory tract, residue in the reticulo-endothelial system and later directly attacks the cardiomyocytes (prime target) via Coxsackie-adenovirus receptor (CAR). On the other hand, erythrovirus (parvovirus B19) or human herpes virus 6 after primarily infection in childhood and asymptomatic long-term residence in the bone marrow and nerve's surroundings, respectively may infect vascular endothelial cells (ECs) and progress to endothelial dysfunction [2, 3, 4].

Based on animal models, the progression of acute cardiac inflammation to DCM is the three-phase process:

– viral (cytopathic) phase – after virus enters target cardiac cells either cardiomyocytes (Coxsackie) or ECs (parvovirus B19), through direct cytopathic injury cause acute cardiac damage, "leakage" of proteins, and exposure of intracellular antigens such as cardiac myosin. There is an extensive viral replication in myoctes that leads to irreversible damge and necrosis/apoptosis.

– (auto)-immunulogic phase – as a result of extensive cardiac damage, immunologic system is activated. Primary (innate) immune response is initiated that is mediated through highly conservative toll-like receptors (TLRs) and results in the activation of nuclear transcription factor kappa (NKF). The effect of which is a massive production of inflammatory cytokines, such as transforming nuclear factor alpha (TNFα) or interleukin (IL-1β) that attracts immunologic cells, such as natural killers cells (NK) and later moncytes, macrophages and neutrophiles. All those signals activate secondary (acquired) immunologic response that is mediated through T and B lymphocytes. Stimulated CD8+ T-cells directly destroy viral particles as well as infected myoctes, whereas B-cells massively produce specific antibodies directed against viral antigens.

– recovery or myopathic phase – in most patients this high-grade inflammation is effective and virus is cleared without any other squeal. However, in some patients with probably predisposing immunologic background, the virus is not cleared but causes ongoing heart-specific inflammation because of mistaken recognition of heart antigens as viral ones. Due to lack of control of immune system and molecular mimicry between viral and endogenous proteins, over-production of auto-antibodies against cardiac antigens such as α-myosin, β1-adrenergic receptors, or laminins further damage the heart. Necrosis and apoptosis of heart tissue stimulates fibrotic process, which eventually lead to remodeling and depression of contractile function.

Based on the presented pathology and results of EMB, myocardits can be further differentiated into [1]:

– **viral myocardits** – simultaneous presence of histological evidence for myocardits and positive viral polymerase chain reaction (PCR)
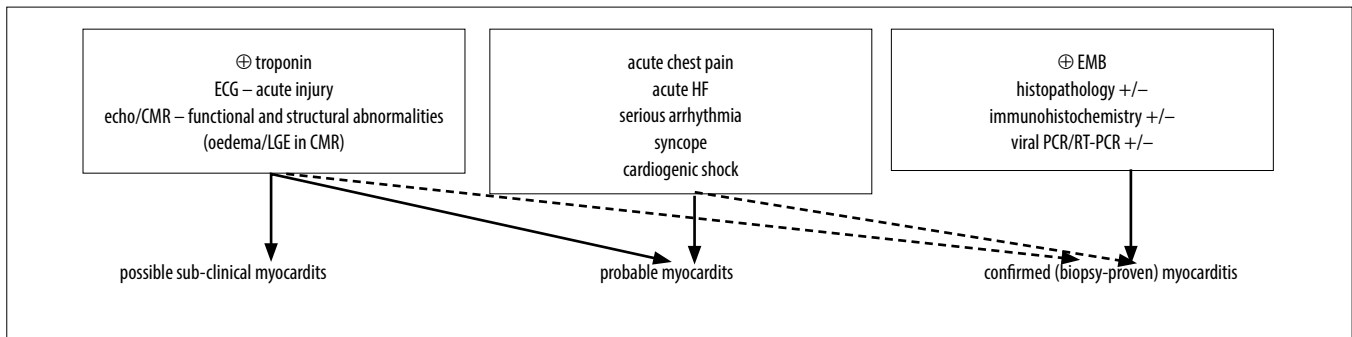
Figure 1. Diagram depicting degree of confidence during myocardits diagnostic work-up

– **autoimmune myocarditis** – which is described as a histological myocardits with negative viral PCR, with or without cardiac autoantibodies
– **viral and immune myocarditis** – simultaneous presence of histological evidence for myocardits, positive viral PCR and cardiac autoantibodies
– **inflammatory cardiomyopathy** – is defined as myocardits in association with cardiac dysfunction.

Clinical symptoms

The majority of viral infections are asymptomatic or oligosymptomatic and patients frequently report a typical viral prodrome with fever, myalgia, and respiratory or gastrointestinal symptoms. Myocardits can occur at any age but young individuals are particularly prone to the disease. Cardiac symptoms are variable and include reduced functional capacity due to dyspnoe and/or fatigue, palpitations, precordial chest pain which result from associated pericarditis or coronary artery spasms [1, 3, 4]. Moreover, there are important ancillary findings, such as fever $\geq 38^0$C at presentation or within the preceding 30 days with or not concomitant symptoms from respiratory (chills, headache, muscle aches, general malaise) or gastrointestinal (decreased appetite, nausea, vomiting, diarrhoea) tract, peri-partum period, previous myocarditis, personal and/or family history of asthma, other types of allergy, extra-cardiac autoimmune diseases, toxic agents or family history of myocardits or DCM. The clinical course of myocarditis ranges from sub-clinical disease to SCD. The clinico-pathologic classification, based on histologic and clinical features, distinguish four types of myocarditis – fulminant, acute, chronic active, and chronic persistent myocarditis. The main difference relies on the onset of symptoms, which is abrupt and clearly defined in fulminant myocarditis but less distinct in other subtypes. Except for rare cases of fulminant myocarditis which result in death, the most important complication of myocarditis is DCM and subsequent chronic heart failure.

Diagnosis

Diagnostic work-up in myocarditis is multistage and requires integration of clinical symptoms, laboratory and imaging data, all of which have rather adjunctive role to the EMB, which is final and ultimately decisive diagnostic tool. After exclusion of typical acute disorders, such as acute coronary syndrome, pulmonary embolism or exacerbation of chronic heart failure (HF), clinical suspicion of myocardits should rise the following presentations: acute chest pain (pericarditic or pseudo-ischaemic), new-onset (acute or subacute, including cardiogenic shock) HF, unexplained serious arrhythmia, or syncope [1]. Clinically suspected myocardits should be confronted with basic diagnostic modalities, such as electrocardioram (ECG), laboratory tests, echocardiography, and if feasible cardiac magnetic resonance (CMR). With the increasing confidence of the working-diagnosis of myocardits, invastigators from the Mayo Clinic have described three diagnostic scenarios (Figure 1) [2].

Electrocardiogram – diagnostic criteria

Although ECG is rarely normal in myocarditis but observed changes are neither sensitive nor specific, and include I[st] to IIIrd degree atrio-ventricular, or bundle branch block, various ST-T wave changes, reduced R wave height, abnormal Q waves, sinus arrest, frequent premature beats, supra-ventricular tachycardia, atrial fibrillation, and lastly ventricular tachycardia or fibrillation.

Laboratory examinations – diagnostic criteria

Inflammatory markers
Both erythrocyte sedimentation rate and reactive C protein are usually increased but normal values do not exclude myocardtits.

Troponins and natriureitc pepatides
Significant increase of cardiac troponins indicate myocytes injury, whereas mild elevation may be a consequence of arrythmias. Elevated serum level of natriuretic peptides is a result of increased ventricular strain and may be a marker of overt HF.

Viral antibodies

Although positive viral serology is frequently observed in myocardts, nevertheless, their diagnostic yield is limited because the presence of circulatory IgM or IgG antibodies directed against viruses is high in the general population.

Serum cardiac autoantibodies

There are more than thirty autoantibodies directed against various cardiac epitopes, such as beta-adrenergic and muscarinic receptors, myosin, tropomyosin, troponins, or laminins. The presence of serum autoantibodies and lack of viral genome in cardiac tissue suggests immune-mediated myocarditis. Furthermore, detection of cardiac autoantibodies have also therapeutic consequences as beneficial effects of therapies directed against antibodies, such as immunsupression, immunomodulation or immunoadsorption were observed.

Echocardiogram – diagnostic criteria

All patients with clinically suspected myocarditis should undergo detailed echocardiographic examination to rule out other cardiac diseases and to assess and monitor changes in chamber size, wall thickness, ventricular systolic and diastolic function, or pericardial effusions.

Cardiac magnetic resonance – diagnostic criteria

CMR is superior to echocardiography in terms of non-invasive tissue charactrization. Whenever possible and feasible, CMR should be performed prior to EMB. International Consensus Group on CMR diagnosis of myocardtis have issued detailed recomndations, known as Lake Louise criteria. Acording to Lake Louise Criteria myocarditis is highly probable when more than 2 of the following criteria are present: a) global T2-SI (signal intensity) ratio ≥2.0, b) global EGE (early gadolinium enhancement) ratio ≥4 and c) ≥1 focal non-ischemic LGE (late gadolinium enhancement) lesion [5]. Recent studies showed that the presence of LGE is an important, negative prognostic factor both in myocarditis and DCM but the role and meaning of LGE is still the subject of the research. However, it should be clearly acknowledged that CMR should not replace or delay EMB in the diagnosis of myocarditis, especially in life-threatening situations.

Endomyocardial biopsy

In clinically-suspected myocarditis, that is consistent with findings from non-invasive studies, it is recommended to perform coronary angiography and EMB. The role of endomyocardial biopsy (EMB) in the management of cardiovascular diseases had been previously defined by the joint scientific statement from the American Heart Association (AHA), the American Collage of Cardiology (ACC), and the European Society of Cardiology (ESC) [6]. According to this document, EMB should be used in one of fourteen possible clinical scenarios in which the prognostic and diagnostic value of the information obtained outweights the risk of the procedure. More than two decades ago Investigators from the US Myocarditis Treatment Trail developed the working standard for the histologic analysis and interpretation of EMB samples, called the Dallas criteria [7]. However, there are many concerns on the accuracy and utility of the histologic evaluation, as the sensitivity of EMB for myocardtitis using the Dallas criteria is low at 10 to 35% [8]. Numerous reasons limit the value of "classic" EMB and include focal and transient nature of inflammatory process, right ventricular (RV) EMB of interventricular septum was preferable site of biopsy regardless the fact that most common site of focal involvement is epicardial surface of the LV free wall, sampling error, last but not least variability of interpretation between even expert pathologists [9, 10].

Therefore, the recent recommendation on myocarditis have re-evaluated EMB in the clinical picture of myocarditis [1]. Moreover, the previous guidelines were based on incomplete assessment of cardiac samples, mainly on the histopathologic Dallas criteria, and did not include immunohistochemistry and viral genome analysis.

The current guidelines provide clear recommendations on cardiac sample handling, e. g. each sample of 1–2 mm in size should be taken, and immediately fixed in 10% buffered formalin for light microscopy; at the same time additional samples should be snap frozen in liquid nitrogen and stored at -80⁰C or stored in RNA later tubes at room temperature for viral PCR. Moreover, samples should be prepared for immunohistochemistry and stained with appropriate monoclonal and polyclonal antibodies (anti-CD3 for T-lymphocytes, anti-CD68 for macrophages, and anti-HLA-DR) [1, 5, 9]. Lastly, of paramount importance is that tissue samples should be assessed by expert pathologists, trained in the assessment of endomyocardial bioptates in the certified laboratories.

Although rare, complications of EMB may occur and are sub classified into major complications which include pericardial tamponade with hemodynamic compromise and requirement for pericardiocentesis, hemo- and pneumopericardium, permanent high-grade atrio-ventricular block requiring pacemaker implantation, myocardial infarction, transient ischemic attack (TIA) and stroke, severe tricuspid valve damage, and death, whereas minor complications include transient chest pain, transient ECG abnormalities, transient arrhythmias, transient hypotension, and small pericardial effusions [6]. The overall complication rates range from less than 1 to as high as 6 percent [6]. However, two recently reported EMB safety studies reported lower rates of complications. In 755 patients with myocardtitis or DCM the major complication rate for left ventricular EMB (LV-EMB) was 0.64% and for RV-EMB was 0.82%. Interestingly, in contrast to common assumptions and earlier reports LV-EMB was not associated with grater risk of complications than RV-EMB [11]. In larger study comprising of 6800 consecutive patients the overall incidence of complications was 1.2%, with myocardial perforation in 0.42% and death in only 0.03% [12].
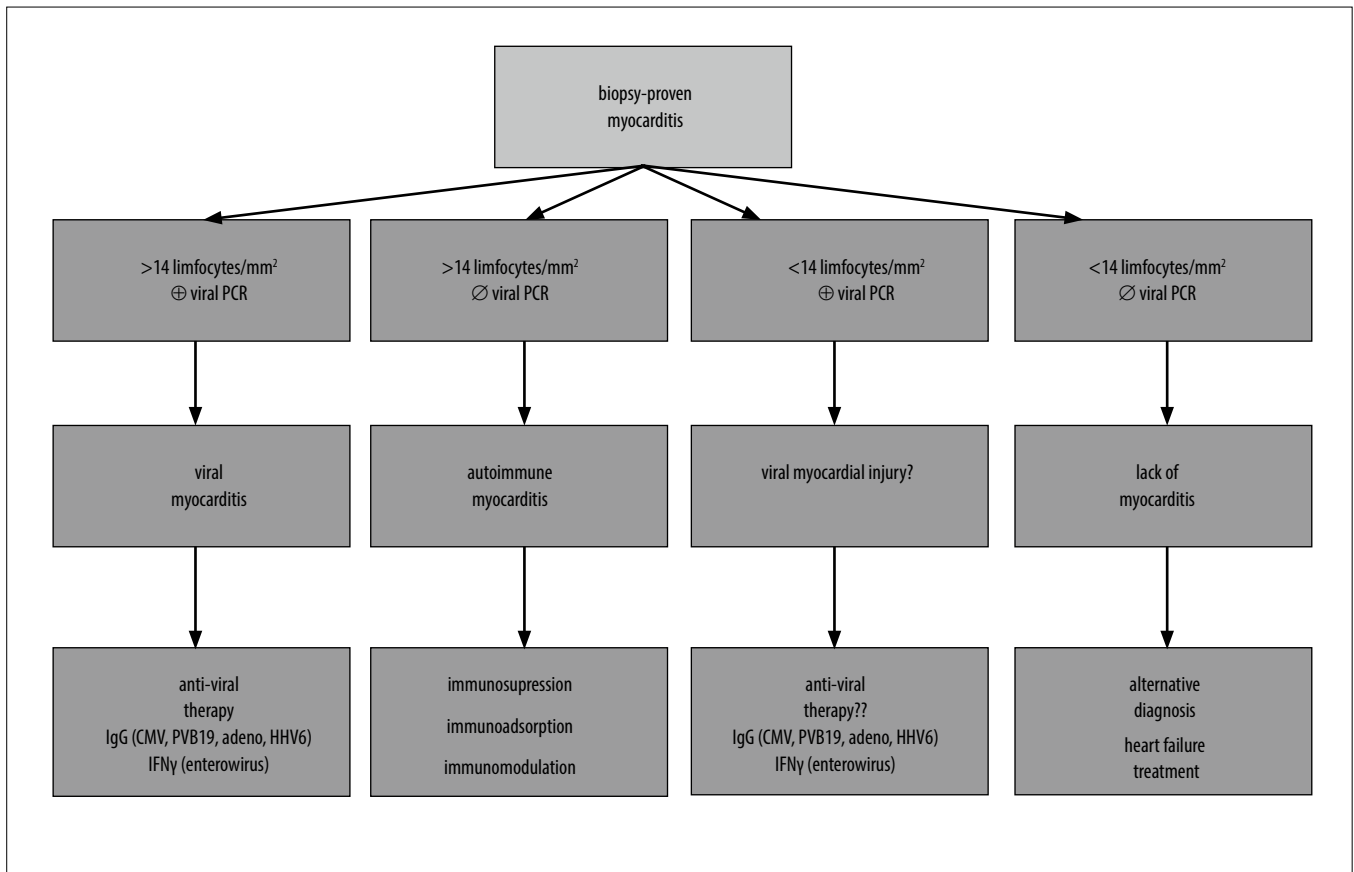
Figure 2. The simplified diagnostic and therapeutic algorithm in myocarditis

Management of myocarditis

General management

It is postulated that patients with suspected myocardits should be sent to the specialized centers with the capability for hemodynamic monitoring, cardiac catherization, and expertise in EMB. In hemodynamically unstable patients, the priority is to stabilize cardiac and respiratory function by means of mechanical cardio-pulmonary support facilities (ventricular assist devices, extracorporeal membrane oxygenation) in intensive care units. Management of stable patients but with cardiac dysfunction should be in line with the current ESC guidelines on HF [13]. Importantly, after initial stabilization, in the long recovery period physical activity should be limited for at least 6 months.

Myocarditis specific therapies

Recent trails have provided substantial body of evidence for additional myocarditis specific or tailored therapies, including anti-viral and immunosupressive therapy. What is of paramount importance that those kind of therapies can be only initiated after state-of-the-art assessment of cardiac samples harvested during EMB and only results of those tests should determine the type of therapy [1]. The simplified diagnostic and therapeutic algorithm is presented below in figure 2.

Anti-viral therapy

Despite significant advancement in the understanding of the viral myocarditis pathology, currently there is still no approved specific anti-viral therapy. However, on the daily basis numerous drugs are used with clear or less clear benefits. There are three drugs, such as acyclovir, gancyclovir, and valacyclovir that are frequently used in herpes virus infection. Promising results have been showed for interferon-beta treatment in patients with LV dysfunction and confirmed enteroviral or adenoviral myocarditis.

High dose intravenous immunoglobulin (IVIG)

Treatment with high dose IVIG has several potential targets, including modulation of immune and inflammatory response, and had been long used in various systemic autoimmune diseases. The benefits of IVIG in myocarditis are less clear but there were several reports on the improvement of LV systolic function in patients with myocarditis.

Immunoadsorption

Various auto-antibodies are present in myocarditis, particularly in later stage. Their role has not been equivocally defined but at least some of them have been proved to be pathogenic. Therefore, the theoretical concept of eradication of those auto-antibodies, with either immunoadsorption or neutralization, seems to be attractive. Initial small series of studies have shown some benefit of

immunadsorption, however, no clear recommendation is given before the results of ongoing large randomized trails will be avaliable.

Immunosupression

Immunosupressive medicines, such as steroids, azathioprine, cyclosporine A and their combinations have been tested in myocarditis. What is known for sure that immunsupression is beneficial and can only be used in virus-negative myocarditis. Initial disappointing effects of immunsupression in widely cited the Myocarditis Treatment Trail are best explained by the fact that patients with myocarditis of unknown etiology were recruited (there were probably many patients with active replication of viral genomes). The best effect of immunosupression was observed for the combination of steroid and azathioprine.

Prognosis of myocarditis

In majority of patients myocaritis will resolve spontaneously in the first 2–4 weeks. However, approximately one-third of patients will develop persistent heart impairment and up to one-quarter may acutely decompensate and die or slowly progress to inflammatory DCM. Furthermore, recent studies have provided conflicting data on the persistence of viral genomes in the myocardium. Some studies reported worse 10-year prognosis in those patients with persistent viruses in comparison to those who had complete viral genome clearance, whereas, there are also reports that provided data on the neutral prognostic role of viruses [1, 3].

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