

Advances in myocarditis management in the light of the latest research and recent guidelines of the European Society of Cardiology

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Abstract

Myocarditis remains an unknown disease with varying clinical manifestations, often leading to heart failure. The latest 2021 and 2022 guidelines of the European Society of Cardiology (ESC) are the first official European documents updating knowledge on the diagnosis and treatment of myocarditis since the 2013 ESC expert consensus statement. These guidelines and new studies allow standardization and improvements to the management of myocarditis. In this review, we discuss the most important aspects of myocarditis diagnosis, therapies and follow-up based on current knowledge. (Cardiol J)

Keywords: cardio-immunology, heart failure, inflammatory cardiomyopathy, immunosuppression, endomyocardial biopsy, personalized medicine

Introduction

Myocarditis/inflammatory cardiomyopathy remains an understudied disease with various clinical manifestations, often leading to heart failure (HF). Moreover, an increase in morbidity and mortality from myocarditis has been recorded in recent years [1, 2]. Myocarditis significantly increases the risk of HF, serious arrhythmias, conduction abnormalities, sudden cardiac death (SCD), anxiety, depression, and it reduces the quality of life [3]. Myocarditis occurs mainly in young adults (18–40 years old) and children; thus, it affects people who study, work or lead active family lives [4].

In recent years, there was a lack of a unified approach to the diagnosis of myocarditis, especially

as demonstrated by the COVID-19 pandemic. All cases resembling myocarditis were diagnosed as myocarditis without a confirmation by endomyocardial biopsy (EMB) or autopsy [5].

Recent (2021 HF, 2022 cardio-oncology, 2022 prevention of SCD) guidelines of the European Society of Cardiology (ESC) are the first official documents updating the knowledge on the management of myocarditis since the 2013 ESC expert consensus statement [6–9]. These guidelines and new research allow standardization and improvements to the diagnosis and treatment of myocarditis. In the following paper, a summary is presented of the most important aspects in the management of myocarditis based on current knowledge (Central illustration) [6].

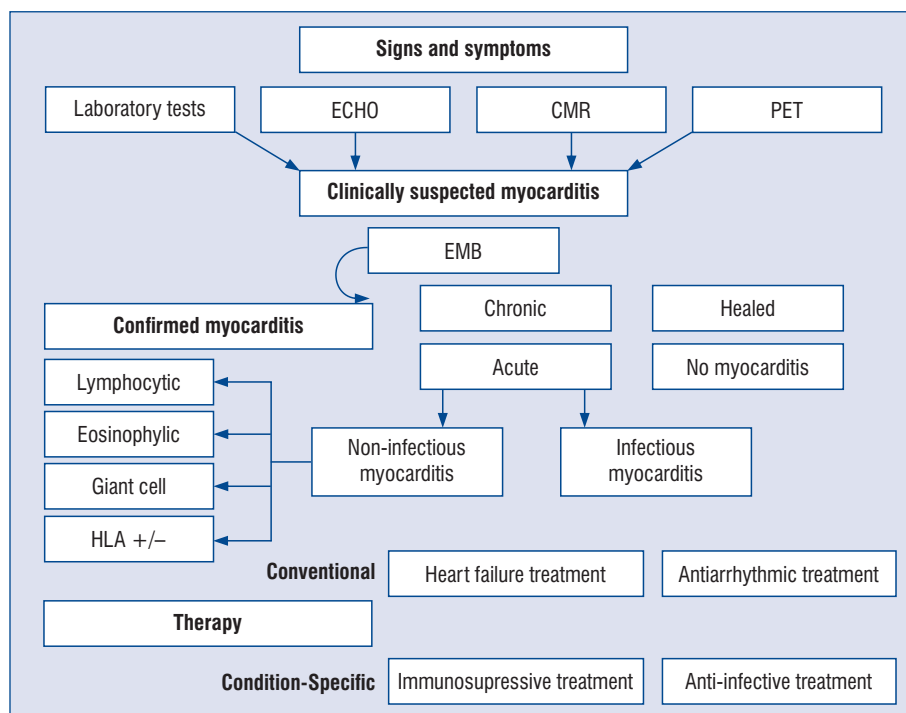
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Central illustration. Personalized diagnostics and treatment of myocarditis; CMR — cardiac magnetic resonance; ECHO — echocardiography; EMB — endomyocardial biopsy; HLA — human leukocyte antigen; PET — positron emission tomography.

Table 1. Myocarditis etiologies.

Etiology	Examples
Infections	Viral: adenoviruses, echoviruses, enteroviruses (e.g., Coxsackieviruses), herpes viruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus (HIV), influenza A virus, parvovirus B19, SARS-CoV-2
Autoimmune	Bacterial, fungal, protozoal, rickettsial, spirochetal, helminthic Hyper eosinophilic syndrome, Kawasaki disease, lupus erythematosus, rheumatoid arthritis, scleroderma, ulcerative colitis, celiac disease, Churg-Strauss syndrome, Crohn’s disease, dermatomyositis
Hypersensitivity reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyl dopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Immune checkpoint inhibitors, amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab
Others	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

Etiology based management

The etiology of myocarditis is often unclear, nonetheless, knowing the causative factor frequently determines patient outcome. The leading causes of myocarditis are infectious agents, systemic diseases, drugs, and toxins (Table 1). The immunohistological assessment characterizes

inflammatory processes by the type of infiltrating cells into lymphocytic, eosinophilic, giant cell myocarditis or cardiac sarcoidosis. To date, infectious etiology should always be assessed during heart tissue examination. However, continuing evidence suggest that in the majority of cases cardiomyocyte injury is caused by immune-mediated reactions activated by viruses, and not by direct virus cell-

Table 2. Recommended diagnostic tests in patients with suspected myocarditis.

Clinical manifestation	Chest pain, dyspnea, signs of left and/or right heart failure, and/or arrhythmias or sudden cardiac death
Diagnostic tests	
ECG	Novel ST-T abnormalities, atrial or ventricular arrhythmias, atrio-ventricular blocks, QRS abnormalities
Laboratory tests	Increased troponins with dynamic fluctuations C-reactive protein or erythrocyte sedimentation rate often increased but non-specific Raised concentrations of brain natriuretic peptides and circulating cytokines Diagnostic tests for specific infective factor Viral serology — low efficacy due to high rate of IgG antibodies against cardiotropic viruses in the general population Anti-heart autoantibodies — may help personalize diagnosis, treatment, and therapy monitoring. So far, it has been used in a limited number of centers [69, 70]
Echocardiography	New regional wall motion abnormalities or global ventricular dysfunction Elevated wall thickness caused by myocardial edema, pericardial effusion, intracardiac thrombi
CMR	Inflammation, edema, and fibrosis detection through T1 and T2 mapping, extracellular volume assessment and LGE
ICA or CTCA	To rule out significant coronary artery disease
EMB	Necessary for definite diagnosis and personalized treatment. May be useful in treatment monitoring
Cardiac PET	May be useful in patients with suspected systemic autoimmune disease or cardiac sarcoidosis and with contraindications to CMR

Definition of suspected myocarditis: clinical manifestation + ≥ 1 obligatory positive test and no coronary artery disease, valvular, congenital heart disease or other disease that could explain the symptoms; CMR — cardiac magnetic resonance; CTCA — computed tomography coronary angiography; ECG — electrocardiography; EMB — endomyocardial biopsy; ICA — invasive coronary angiography; LGE — late gadolinium enhancement; PET — positron emission tomography

injury. This may be attributed to molecular mimicry between viruses and cardiac antigens [10].

Autoimmune/immune-mediated myocarditis may occur i.e., during antineoplastic treatment, due to previous infection (without the presence of the infectious agent) or in the course of autoimmune disorders with extra-cardiac presentations, e.g., sarcoidosis, hypereosinophilic syndrome, scleroderma, granulomatosis with polyangiitis and systemic lupus erythematosus (Table 1) [6]. In some cases, cardiac involvement may be the only manifestation of an autoimmune disorder [11].

Novel cardio-oncology ESC guidelines define cancer-therapy-related cardiovascular toxicity for example immune checkpoint inhibitors-associated myocarditis [8]. Immune checkpoint inhibitor-myocarditis most often appears in the first 12 weeks of the therapy; however, it can also appear after 20 weeks [12].

Moreover, research suggests that there may be a genetic liability to myocarditis. For example, a genetic alteration in the desmosome may predispose one to the spread of an infectious agent and development of the disease [13]. In patients

with HF and left ventricle (LV) dysfunction and EMB proven myocarditis, about 30% of patients had pathogenic variants of cardiomyopathy causing genes like *Titin* [14]. The search for the etiology of the disease is a key element that provides the opportunity to implement disease-directed treatment [15].

Diagnosics of myocarditis

Clinically suspected vs. true myocarditis

The clinical presentation of patients with myocarditis is diverse. It ranges from asymptomatic cases, chest pain and palpitations with transient electrocardiogram (ECG) changes, to life-threatening cardiogenic shock and ventricular arrhythmias. The diagnosis is made based on the clinical picture and preliminary abnormalities in additional tests (Table 2). Recent HF guidelines highlight that myocarditis should be suspected when there is a clinical presentation and ≥ 1 mandatory diagnostic test (by preference cardiac magnetic resonance [CMR]) comes out positive (Table 2). CMR should be performed to assess cardiac function, structure,

and tissue characterization in every patient with suspected myocarditis [6].

A combination of methods including CMR, and troponin levels improves the diagnostic accuracy [16]. It is also necessary to rule out significant coronary artery disease or extra-cardiac causes of symptoms (by invasive coronary angiography or computed tomography) [6].

Patients with clinically suspected acute myocarditis usually present with recent symptoms (i.e. chest pain, palpitations) and signs of acute myocardial injury (electrocardiographic changes, elevated troponin levels). Elevated cardiac troponin levels are an important sign of myocyte injury and should always be assessed. However, troponin elevation is not always present in patients with clinically suspected myocarditis, especially in the chronic stage of the disease [17]. Other biomarkers of cardiac injury or inflammation (e.g., C-reactive protein level) are not specific and, therefore, their testing is not recommended.

Patients with suspected chronic myocarditis usually present with signs of chronic HF. Additionally, myocarditis may cause raised concentrations of brain natriuretic peptides, circulating cytokines and markers related to extracellular matrix degradation, but these biomarkers have no clinical utility in the diagnosis of myocarditis. Despite recent advances in non-invasive methods, true myocarditis may only be confirmed by EMB or autopsy [6].

Electrocardiogram

Electrocardiogram is usually abnormal in patients with HF as well as with myocarditis [18]; however, the changes are not specific for myocarditis.

Myocarditis may be suggested mainly by concave and diffuse ST-T segment elevation, as well as atrial and ventricular arrhythmias. Atrioventricular and/or intraventricular conduction abnormalities may reflect e.g., laminopathy, Lyme disease, cardiac sarcoidosis, giant cell myocarditis and/or diffuse and advanced inflammatory processes [19].

Echocardiography

Echocardiography should be performed in every patient to exclude other, non-inflammatory causes of symptoms, evaluate cardiac morphology, and function, and assess potential complications (fluid, thrombi, valvular regurgitations). Additionally, echocardiography (ECHO) is the best imaging tool for non-invasive monitoring of the course of the disease. Modern techniques such as speckle tracking echocardiography (STE) may identify

patients with subclinical myocardial dysfunction at an early stage of the disease. Therefore, STE should be recommended in the diagnostic process of suspected acute myocarditis, especially in patients with initially preserved LV ejection fraction (LVEF). STE has high sensitivity and may be correlated with EMB results and novel CMR techniques [20]. Moreover, STE may be used for the prognosis of a worse myocardial function in long-term follow-up [21].

Cardiac magnetic resonance

Cardiac magnetic resonance imaging with diagnostic requirements defined by the Lake Louise Criteria (LLC) updated in 2018 is the non-invasive test of choice [22]. CMR enables the assessment of cardiac morphology and function. It also offers a unique opportunity for myocardial tissue characterization, necessary for differential diagnosis. The LLC are based on the following CMR features: tissue edema, hyperemia, necrosis, or fibrosis, which vary along with either acute or chronic phases of myocarditis. Updated LLC criteria include a new CMR technique, i.e. parametric T1 and T2 mapping [23]. According to novel LLC, the diagnosis of myocarditis requires at least one T1-based criterion (presence of late gadolinium enhancement [LGE] in non-ischemic pattern distribution, increased myocardial T1 relaxation times or extracellular volume values) and at least one T2-based criterion (visible myocardial edema [hyperintensity in T2 weighted short tau-inversion recovery], increased myocardial T2 relaxation times, or T2 signal intensity ratio) [24].

The updated CMR LLC include parametric mapping as the reference noninvasive method for the diagnosis and prognosis of myocarditis [22, 23]. Novel CMR mapping techniques generate pixel-wise, quantitative maps of the myocardium. Therefore, quantitative parametric mapping improves sensitivity in showing inflammation, edema, and fibrosis in contrast to typical T1 and T2 imaging CMR techniques [25, 26].

Its prognostic role is also an additional advantage of CMR. The presence of LGE is associated with a worse prognosis and higher risk of all-cause mortality, HF hospitalization, arrhythmias, and SCD [27]. Grun et al. [28] have shown that the presence of LGE was associated with 8.4–12.8-fold increased all-cause and cardiac mortality in a group of 202 patients with EMB-proven viral myocarditis over 4.7 years of follow-up. Primary LGE is a prominent predictor of outcomes, i.e., all-cause mortality, cardiovascular death, SCD,

cardiac transplantation, appropriate implantable cardioverter-defibrillator (ICD) shock, and recurrence of myocarditis, regardless of LVEF [28]. Another study, (n = 1,672 patients with dilated cardiomyopathy [DCM]) have demonstrated a 1.5-fold increased risk for all-cause mortality, heart transplantation, or left ventricular assist device implantation in patients with LGE presence over a median follow up of 2.3 years [29].

The location of LGE is also of importance. The non-ischemic LGE pattern in epicardial, midwall regions or insertion points has been linked with the diagnosis of myocarditis [30]. The patients with acute myocarditis and LGE in the midwall layer of the anteroseptal myocardial segment have a worse prognosis in contrast to other patterns of presentation [31]. One of the studies has shown LGE involvement in midwall and septal regions to be associated with a higher risk of major adverse cardiac events [32]. Another study from Mahrholdt et al. [33] has also confirmed that LGE involvement of the septal wall predicts persistent LV dysfunction, although LGE involvement of the lateral wall is associated with superior outcome during follow-up.

A favorable outcome and recovery involve a complete resolution of inflammation or persistence of both LGE and edema, contrary to the persistence of LGE and disappearance of edema which are associated with a worse prognosis [34]. Moreover, persistent LGE identifies patients not completely responding to treatment and it may be a changing factor for intensified medical treatments or procedures such as ICD implantation [35].

A follow-up CMR a few months after the acute/initial episode of myocarditis may have a prognostic value and is recommended particularly in patients willing to return to physical activity. A possible reduction of LGE extent, resolution of inflammation and changes in LVEF should be assessed. Reduced LVEF and high degree of LGE at admission are negative prognostic factors. Therefore, patients with decreased LVEF at baseline should be closely monitored with follow-up CMR at 3 to 6 months due to the possibility of LV dysfunction [36].

Some CMR limitations should be considered in clinical evaluation. CMR has an especially high diagnostic value in acute myocarditis, but its sensitivity in chronic myocarditis is significantly limited. What is more, failure to fulfill the LCC criteria does not exclude myocarditis just as a confirmation of myocarditis on CMR images does not allow for the assessment of the etiology of myocarditis, viral status, and definitive confirmation of myocarditis.

Nuclear techniques

Single-photon emission computed tomography may be performed to determine myocardial viability, inflammation, and infiltration [6].

¹⁸F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is a novel imaging technique which may improve diagnostic accuracy. It can determine the inflammation of the myocardial tissue by increased glucose uptake in the inflamed areas. Since CMR accuracy is low in chronic myocarditis, FDG-PET may be applicable in those cases, and be complementary to CMR [37].

Endomyocardial biopsy

Endomyocardial biopsy is a gold standard and provides a definitive diagnosis of myocarditis. The EMB allows for the assessment of the specific histotype, immunologic and virologic status of the myocardium with immunohistochemistry and polymerase chain reaction analysis [38].

The latest ESC HF guidelines recommend EMB in patients with severe cardiac impairment and/or serious ventricular arrhythmias or atrio-ventricular blocks [6]. In patients not responding to standard HF and antiarrhythmic therapy in a short time, EMB should be performed for a better insight of the HF mechanism and the diagnosis of possible ongoing myocarditis (Table 3). Therefore, an approach with the use of EMB allows for a personalized and specific treatment due to the identification of disease etiology, particularly in case of giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, and systemic inflammatory disorders. EMB can be repeated in case of unexplained progression of HF or to monitor response to treatment (Table 3) [6].

At least 5–7 samples should be obtained to ensure the best accuracy and precise immunohistologic and molecular evaluation. There is no preference regarding left or right ventricular EMB. However, if possible, biventricular EMB should be performed. Biventricular EMB provides an improved diagnostic and prognostic accuracy, especially in the detection of suspected cardiac sarcoidosis or giant cell myocarditis [6]. The latest ESC guidelines on the management of ventricular arrhythmias and prevention of SCD recommended a novel approach using mapping-guided biopsy to provide the diagnosis in patients with focal myocardial involvement in CMR [9]. Endocardial electroanatomic mapping may be beneficial for targeted EMB, particularly in patients with suspected cardiac sarcoidosis or giant cell-myocarditis [9].

Table 3. Recommendations for endomyocardial biopsy in patients with suspected myocarditis [6, 38].

Recommendations for endomyocardial biopsy	Class of recommendation
In case of acute/fulminant myocarditis with progression or persistent cardiac dysfunction and/or malignant ventricular arrhythmias and/or atrioventricular block without expected response to standard treatment during first < 1–2 weeks	I
In patients with exacerbation of heart failure despite optimal treatment when there is a suspicion of specific diagnosis which can be confirmed in myocardial samples	IIa
Endomyocardial biopsy is especially recommended in patients with acute and/or chronic heart failure and suspected giant cell-, eosinophilic-, immune checkpoint inhibitor-related and/or lymphocytic myocarditis, vasculitis, sarcoidosis, systemic lupus erythematosus, and other auto-immune conditions	I

Of note, EMB rate of major complications is lower than 1% if it is performed by experienced cardiologists. Biventricular EMB is also a safe procedure with a low complication rate [39].

Treatment options

For the first time, the latest ESC HF guidelines offer a detailed approach to patients with myocarditis. Treatment of myocarditis should be based on clinical presentation, disease stage and if known — disease etiology [6]. Around 50% of cases of acute myocarditis resolve spontaneously in weeks after onset, 25% of cases transform into permanent heart dysfunction and approximately 25% deteriorate or progress to DCM with a need for heart transplantation or other form of ventricular support [40, 41]. Factors such as symptomatic HF, presence of ventricular arrhythmias, atrioventricular and/or bundle branch block, low LVEF at baseline, and fulminant course of the disease predict a worse prognosis [42]. As highlighted by the current guidelines, individual therapy of myocarditis should be based on EMB findings [6]. This applies to immunosuppressive or anti-infective treatment, as well as to the monitoring of therapy.

Supportive treatment

The main goal of treatment is the optimal management of HF and arrhythmias according to standard recommendations from appropriate guidelines. According to the ESC guidelines, standard HF therapy with angiotensin converting enzyme inhibitors or angiotensin receptor neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists and sodium glucose co-transporter type 2 inhibitors should be initiated when baseline LVEF is decreased [6]. Patients after myocarditis with improved ejection fraction (EF) meaning

patients with previous HF with reduced EF and now with an EF more than 40% should continue HF therapy [43].

Moreover, hemodynamically unstable patients with acute/fulminant myocarditis (FM) should be treated in experienced intensive cardiac care units with respiratory and mechanical circulatory support, if necessary [6]. Patients with FM and deteriorating cardiac function may require diuretics, inotropes, and vasopressors. In case of cardiogenic shock unresponsive to initial treatment, temporary mechanical ventilation, veno-arterial extracorporeal membrane oxygenation or the Impella heart pump should be considered [44]. Heart transplant or left ventricular assist device implantation should be under consideration when transient mechanical circulatory support must be continued for more than 2 or 3 weeks [45, 46].

Prevention of SCD

In patients with myocarditis, it is recommended to assess individually the indications for ICD or cardiac resynchronization therapy (CRT). ICD implantation in primary SCD prevention is not advised in the acute phase of myocarditis. The decision should be delayed for 3 to 6 months. Of note, in patients with a high risk of arrhythmias and/or serious left ventricular dysfunction a wearable cardioverter defibrillator may be beneficial as a bridge to an implanted device, cardiac transplantation, or resolution after immunosuppressive treatment [6]. Although, if sustained ventricular tachycardia or ventricular fibrillation is hemodynamically not tolerated, ICD implantation should be considered even in the acute phase of myocarditis [47, 48]. In patients with chronic myocarditis or post-myocarditis if ventricular tachycardia is recurrent, the administration of amiodarone or catheter ablation (when amiodaron is not effective or not tolerated) and/or ICD implantation should be considered [9].

Anti-cancer treatment related myocarditis

The management pathway of suspected/confirmed myocarditis related to antineoplastic treatment should be based on its interruption, hospital admission and detailed diagnostic workup. In patients with suspected immune checkpoint inhibitor-associated myocarditis treatment with methylprednisolone intravenously for the first 3–5 days and then orally under clinical, ECG, ECHO and cardiac troponin surveillance is recommended [49]. During recovery, a multidisciplinary approach should be applied to review the continuation of the antineoplastic treatment. Complete recovery is defined as a total resolution of acute symptoms, normalization of biomarkers, or decrease in cardiac troponin by 50% from the highest level, and improvement of LVEF after the end of immunosuppressive therapy [50]. LGE or increased T1 signal on CMR may be present but the absence of acute edema should be confirmed [51].

Immunosuppression

For the first time, the new ESC HF guidelines have suggested considering immunosuppressive treatment in EMB-proven cases. Immunosuppression with duration tailored to the disease activity (usually for at least 6–12 months) is recommended in EMB-proven myocarditis, particularly giant cell or eosinophilic myocarditis, cardiac sarcoidosis, and myocarditis (especially FM) triggered by systemic autoimmune diseases [6]. Despite the growing doubts about the role and importance of viruses in myocarditis, it is still not recommended to start immunosuppression in patients without ruling out the presence of a virus in EMB [6, 52]. However, in case of acute HF and/or life-threatening arrhythmias during FM, some experts suggest that empirical therapy with intravenous corticosteroids may be considered without delay when immune etiology is suspected [53]. Giant cell myocarditis is the most aggressive form of autoimmune myocarditis; therefore, high-dose immunosuppression should be administered right after the diagnosis [54]. Eosinophilic myocarditis requires the discontinuation of the responsible agent, and it often responds well to high-dose steroid therapy [55].

There is also promising data on immunosuppressive therapy with prednisone and azathioprine in chronic lymphocytic myocarditis [56]. A significant increase in LVEF and a decrease in LV dimensions and volumes was observed in some single-center studies [57]. Recently, Chimenti et al. [58] published a 20-year follow up of the TIMIC (Tailored IMMunosuppression in virus-negative

Inflammatory Cardiomyopathy) trial that confirmed the lasting benefit of immunosuppressive therapy. However, further, randomized controlled studies are needed to explain the efficacy and safety of the immunosuppressive therapy in myocarditis. At present a multicenter, double blind randomized trial (IMPROVE-MC) on combined 12-month therapy of azathioprine with prednisone is ongoing in Poland [59, 60].

Anti-infection therapy

To date, there is no antiviral therapy that has a proven effect. Nonetheless, targeted antiviral therapy is recommended in confirmed cases of human immunodeficiency virus, cytomegalovirus, or human herpes virus 6 based on viral load and replication activity [6]. In one of the studies treatments with interferon beta in EMB-diagnosed viral myocarditis improved LVEF, quality of life and symptoms based on New York Heart Association class [61, 62].

Viral serology has low efficacy in the diagnosis of myocarditis because the presence of circulatory IgG antibodies against cardiotropic viruses in the general population without viral heart disease is high. Further, a lack of a correlation between virus serology and EMB results has been proven [63].

When other curable infectious diseases, i.e., Lyme disease are diagnosed, specific treatment should be administered [6].

Immunomodulation

The intravenous immunoglobulin (IVIG) treatment is non-established in myocarditis although it has been linked to improvement of LV function in DCM [64]. A recently published meta-analysis of the pediatric population has shown that IVIG treatment improved LVEF and decreased in-hospital mortality with fine tolerance [65]. In contrast, another meta-analysis did not prove an increase in LVEF [66]. Based on current data, IVIG is not routinely recommended as a treatment option in myocarditis or DCM [6].

Return to physical activity and long-term monitoring

Consequently, the assessment of exercise related SCD risk, by means of ECG, imaging studies, exercise stress test and Holter monitoring, is recommended following myocarditis recovery [6]. The assessment should be performed in planned time frames with follow-up at 3–6 months after the acute phase of the disease and then annually for at

least 4 years [6, 67, 68]. Moderate to high-intensity training should be abandoned for at least 6 months till symptoms, increased troponins, or clinically significant ECG/CMR/ECHO abnormalities are persistent. Patients with vast LGE areas (> 20%) and decreased LVEF should not participate in training of a moderate to high intensity. A follow-up EMB to reveal evidence of the resolution of inflammation and healed myocarditis may be considered [6]. Patients with previous myocarditis are at an increased risk for the recurrence of the disease.

Conflict of interest: None declared

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