Myocarditis heart failure: A review of clinical status and meta-analyses of diagnostic performance of cardiac magnetic resonance and therapeutic value of immunosuppressive therapy

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Abstract
Myocarditis heart failure or inflammatory cardiomyopathy is a polymorphic disease complicated by heterogeneous clinical presentation and evolution. Patients with myocarditis presenting with severe left ventricular (LV) dysfunction and life-threatening arrhythmias represent a demanding challenge to clinicians. Although molecular evaluation of the myocardium using endomyocardial biopsy and modern techniques of cardiovascular imaging provide valuable insights into its etiology and pathophysiology, diagnosis remains a clinical challenge because of varied modes of clinical presentation, diversity of approaches to diagnosis, a spectrum of clinical courses and unsettled perspective on therapeutics in different patient settings and viral pathologies. This review seeks to frame recent clinical advances in diagnosing and managing myocarditis HF within the latest understanding of clinical presentation, etiology and pathophysiology obtained from experimental animal models and clinical trials. The objective is to improve understanding of the clinical status of myocarditis heart failure.

Introduction
Heart failure (HF) is the culmination of many forms of heart diseases. It manifests as signs and symptoms suggesting cardiac dysfunction. Objective evidence of cardiac dysfunction is necessary for diagnosis [1], and the identification of the underlying etiology is key to guide diagnostic, therapeutic and prophylactic strategies [2]. However, the current HF classification systems: anterograde vs. retrograde, acute vs. chronic, left vs. right, and systolic vs. diastolic do not focus on the underlying etiology rather on cardiac dysfunction or time of onset [2]. These classification systems motivate research on objective assessment of cardiac structure and function as the basis for diagnosis and treatment. In fact, the leading heart and cardiology societies such as American Heart Association (AHA) [3] and European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases [4] refer to myocarditis as one of the causes of dilated cardiomyopathy (DCM) or a form of inflammatory cardiomyopathy. The consequence is research on myocarditis as a distinct form of HF has lagged far behind that of other common forms of HF. Thus, the present paper reviews published evidence including two meta-analyses of diagnostic performance of cardiac magnetic resonance imaging and therapeutic value of immunosuppression or immunomodulation on patients with myocarditis HF.

Brief history
The seminal description of an inflammatory disease of the heart and the difficulty in its detection appeared in the publication “Treatise on Disease of the Heart” in 1749 by a French physician, Jean Baptiste Senac. Later in 1873, Joseph Friedrich Sobernheim originated the term myocarditis. Initially, the term included other undocumented forms of cardiomyopathies and HF such as ischemic heart disease and hypertensive heart disease [6]. In 1980, the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) made the initial attempt to differentiate between myocarditis, and other forms of cardiomyopathies and HF [7]. Since then, endomyocardial biopsies of DCM patients and studies exploring the natural history of patients with selected conditions such as Chagas disease have established that myocarditis is majorly a viral infection causing immunologic damage to the myocardium culminating in DCM with LV dysfunction [3]. The term has now been refined to apply to acute or chronic inflammation of the heart muscles to environmental or endogenous triggers most commonly viruses and less frequently bacterial, fungi and parasites, and non-infectious causes such as systemic autoimmune responses and drug-induced hypersensitivity [8]. Myocarditis HF has also been referred to as inflammatory cardiomyopathy mainly because myocarditis mainly progresses into HF through DCM. The lack of a uniform terminology complicates comparison of studies across countries or healthcare systems to develop a universal understanding of myocarditis HF.

Definition
Myocarditis is an inflammatory disease of the myocardium frequently caused by a viral infection and/or post-viral immune-
mediated responses [9]. The ESC describes it as an acute inflammatory disorder of the heart muscle often with preserved left ventricular (LV) function [4]. It manifests with a spectrum of symptoms ranging from mild dyspnea to cardiogenic shock and sudden death. Its long-term consequence is DCM with chronic HF [10]. The AHA refers to myocardial HF as inflammatory cardiomyopathy resulting from acute or chronic inflammatory processes affecting the myocardium produced by a variety of toxins and drugs such as cocaine and interleukin 2 or by infection agents mostly viral and/or bacterial, rickettsial, fungal or parasitic [3]. The ESC goes further to describe myocarditis HF by the presence of chronic inflammatory cells (cellular infiltrate and myocyte necrosis) accompanied by LV dilatation and depressed ejection fraction detected by histology and/or immunocytochemistry analyses [4]. Beside toxins and drugs, myocarditis HF may result from autoimmune and systemic diseases such as Whipple disease, giant cell myocarditis (GCM) and hypersensitive reaction to drugs such as antibiotics, sulfonamides, anticonvulsants and anti-inflammatory agents [3].

### Epidemiology

Accurate population-based estimates of the incidence and prevalence of myocarditis HF has been difficult to determine mainly because of widely varying clinical presentation and reduced utility of endomyocardial biopsy due to perceived risks, and the lack of widely accepted and sensitive histologic standards [10]. The wide diversity of clinical manifestations from non-specific symptoms to severe myocardial destruction potentially underestimates the current epidemiological estimates of myocarditis HF [6]. The 2013 global burden of myocarditis report based on hospital dismissal data found the burden of myocarditis as a percentage of HF varies by age and region from 0.5% to 4.0% [5]. In a systematic analysis for the Global Burden of Disease Study 2013, the estimated global prevalence of myocarditis HF was 22 of 100,000 patients annually [12]. A recent scientific statement by the AHA and the American College of Cardiology (ACC) on eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities rank myocarditis HF as the third leading cause of sudden cardiac death (SCD) in competitive athletes [13]. In a study of suspected myocarditis on 672,672 male military recruits (mean age 20 years), 98 had myocarditis mimicking myocardial infarction, one case of SCD and nine cases of DCM in the initial stages of clinical disease [14]. Autopsy studies report an incidence of myocarditis according to population studied ranges between 0.11% and 12% [15-19].

The prevalence of myocarditis HF is higher in men [20-22]. According to mouse model of myocarditis, sex hormones may mediate the differences in gender prevalence of myocarditis HF [23,24]. In female mice, estrogenic hormones protect against viremia (presence of virus in blood) and viral infectivity of cardiomyocytes while decreasing harmful myocardial inflammatory reaction [23]. Conversely, in male mice, testosterone has a detrimental effect via the inhibition of anti-inflammatory response [24]. Current evidence also suggests a higher prevalence in young adults. The mean age of patients with GCM is 42 years [25] and the mean age of adult patients with other forms of myocarditis ranges from 20 to 51 years [26,27]. The consequences in this population are severe. Autopsy reports show myocarditis causes SCD in up to 12% in patients aged < 40 years [19,27,28] and in military recruits [14] and young athletes [13]. Myocarditis has also been associated with higher rates of SCD and cardiomyopathy in pediatric populations [29-31], with the risk of death and heart transplantation persisting up to 12 years [32]. The presence of co-morbidities such as cardiac amyloidosis, hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia have been associated with poor prognosis [33-35].

### Etiology

The position statement from the 2013 ESC Working Group on myocardial and pericardial diseases lists large variety infectious agents, systemic diseases, drugs and toxins as common causes of myocarditis HF (Table 1).

### Viral etiologies

The predominant cause of myocarditis are infectious agents with viral etiologies largely prevailing over other causes as well as represents the most studied etiology of myocarditis HF [36]. In Europe and the United States, Coxackie virus, parvovirus B19, HHV-6 type B and the adenovirus are the most frequently encountered viral etiologies in

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
<th>Examples</th>
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<tbody>
<tr>
<td></td>
<td><strong>Bacterial</strong></td>
<td>Staphylococcus, Streptococcus, Pneumococcus, Meningococcus, Gonococcus, Salmonella, Corynebacterium diphtheriae, Haemophilus influenzae, Mycobacterium, Mycoplasma pneumoniae, Brucella</td>
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<td></td>
<td><strong>Fungal</strong></td>
<td>Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporotrich</td>
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<td><strong>Protozoal</strong></td>
<td>Trypanosoma cruzi, Toxoplasma gondii, Entamoeba, Leishmania</td>
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<td><strong>Parasitic</strong></td>
<td>Trichinella spiralis, Echinococcus granulosus, Taenia solium</td>
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<td><strong>Immune-mediated</strong></td>
<td><strong>Responses</strong></td>
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<td></td>
<td><strong>Allergens</strong></td>
<td>Tetanus toxoid, vaccines, serum sickness, drugs (penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methylpap, thiazide diuretics, amitryptiline)</td>
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<td></td>
<td><strong>Autoantigens</strong></td>
<td>Heart transplant rejection</td>
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<tr>
<td></td>
<td><strong>Drugs</strong></td>
<td>Infection-negative lymphocyte, infection-negative giant cell and immune-oriented disorders (systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki’s disease, inflammatory bowel disease, scleroderma, polymyositis, myocarditis gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener’s granulomatosis, rheumatic heart disease.</td>
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<td></td>
<td><strong>Heavy metals</strong></td>
<td>Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)</td>
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<td><strong>Physical Agents</strong></td>
<td>Radiation, electric shock</td>
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<td></td>
<td><strong>Hormones</strong></td>
<td>Phaeochromocytoma, vitamins: beriberi</td>
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**Table 1. Common causes of myocarditis heart failure**

**HHV:** Human Herpes Virus; **HIV:** Human Immunodeficiency Virus. Adapted from the ESC Working Group on Myocardial and Pericardial Diseases, p.2638 [11]
acute myocarditis in children and young adults (< 35 years) [37-39]. In the past two decades, polymerase chain reaction (PCR) and in situ hybridization in heart biopsy samples have been able to identify a range of other cardiotropic viruses involved in the pathophysiology of myocarditis including H1N1 strains of influenza [40], adenovirus [38,41], Hepatitis C [42,43], human immunodeficiency virus (HIV) [4] and cytomegalovirus, echovirus, parvovirus B-19, and Epstein-Barr virus [45]. In the case of chronic myocarditis, there is absence of data from transverse or longitudinal studies to determine the incidence of various viral etiologies of cardiac infection. However, viral persistence was associated with ventricular dysfunction while viral genome clearance was associated with hemodynamic improvement [37].

Non-viral etiologies

In select populations, specific non-viral infections and autoimmune syndromes have also been implicated as important etiologies of myocarditis [8]. Autoimmune reaction following untreated streptococcal infection may lead to rheumatic carditis [46]. Bacterial infection (diphtheria and borrelia burgdorferi) or parasites (Chagas disease) are important non-viral etiologies in specific regions [47,48]. Hypersensitivity myocarditis may be a consequence of exposure of various drugs, toxins or vaccine-specific cardiac autoimmune responses [8]. Most cases of hypersensitivity myocarditis develop early in the course of drug use but an estimated 15% of clozapine-induced myocarditis may develop later, up to two years following the initiation of drug therapy [49,50]. Vaccination against smallpox infection has also been linked to myopericarditis in up to 6 in 10,000 vaccines [51]. Other non-viral and non-infectious etiologies of myocarditis include cardiac inflammation following exposure to radiation, systemic autoimmune diseases such as antinuclear antibody-related vasculitis, systemic sclerosis, lupus erythematosus, and celiac disease [52].

Pathophysiology

Although the precise pathophysiologic mechanisms of myocarditis in humans is not well established, accumulating evidence suggests it is the result of viral and autoimmune mechanisms acting in the presence of a genetic predisposition (familial) or occurring sporadically [53-57]. However, the bulk of the evidence in the pathophysiology of myocarditis relies on murine models of enterovirus myocarditis. The evidence suggests myocarditis develops in three phases: acute phase, sub-acute phase and chronic phase [58-62] (Figure 1).

Phase I: Acute phase

The initial (or acute) phase begins with entroviruses preferentially entering cardiomyocytes through specific receptors leading to severe cytopathic effect due to virus replication about two weeks post-infection. Consequently, humoral and cellular immune reaction comprising of macrophages, and CD4+ and CD8+ T- lymphocytes are initiated leading to the elimination of the infectious agent within two weeks post-infection in resistant mice strains. In susceptible mice strains, viral RNA and inflammation persists for several weeks [61-62]. The ongoing infection and inflammation triggers autoimmune responses in the heart resulting from cardiomyocyte necrosis and subsequent release of self-antigens previously hidden to the immune system. The susceptible mice strains may develop autoimmune lymphocytic or GCM and later DCM after immunization with cardiac auto-antigens or spontaneously [64]. After viral entry acute injury of the cardiomyocytes induced by virus replication results in cardiomyocyte necrosis, the exposure of intracellular antigens and the activation of host autoimmune response. Autoimmune response increases cardiac cell injury and can result in efficient viral clearance, corresponding clinically to subclinical myocarditis [36]. The acute phase occurs in a few days [9]. In clinical practice, this phase is often asymptomatic [63].

Phase II: Subacute phase

The second (or sub-acute) phase, which covers a few weeks to several months, is characterized by autoimmune reaction. Activated virus specific T-lymphocytes may attack the host's organs by molecular mimicry (some host myocardial cellular antigens sharing epitopic similarities with viral antigens). Cytokine activation (tumor necrosis factor [TNF]-alpha and interleukin (IL)-1 and -6) and antibodies to viral and cardiac proteins may aggravate cardiac damage leading to contractile dysfunction [9,36]. In most patients with myocarditis, immune response decreases with virus elimination and LV function recovers but in some murine models autoimmune responses persists independent of virus genome in the myocardium and could progress into the chronic phase [59].

Phase III: Chronic phase

In the third (or chronic) phase, pathological manifestations of myocarditis disappear and the destroyed cardiomyocytes are replaced by diffuse fibrosis [65]. Autoantibodies to several cardiac antigens are common in patients with myocarditis and DCM and suspected to

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**Figure 1:** Pathophysiology of myocarditis heart failure

Pathophysiology of myocarditis is triphasic. Phase I: Viral infection and replication in the heart inducing innate immune responses. Phase II: Myocardial damage induces autoantibodies and autoimmune T-cells responses via epitope spreading or molecular mimicry. Phase III: Low-grade viral persistence and inflammation causes remodeling contributing to dilated cardiomyopathy. Adapted from Martinez et al., 2012 [63]
precede the development of myocarditis HF. Antibodies acting against beta-1 adrenergic receptors have been found in serum of myocarditis and DCM patients and their removal by immuno-absorption improved cardiac function [10]. In some hosts, molecular mimicry induces an autoimmune trait sustaining the inflammatory reaction to cause chronic inflammation or DCM. This phase is characterized by biventricular dilatation with HF associated with persistent virus or latent endomyocardial replication, dilatation, and contractile dysfunction [66].

**Clinical presentation**

The 2013 ESC guidelines on myocardial and pericardial diseases proposed criteria for raising clinical suspicion of myocarditis HF based on the clinical course of the disease alongside common clinical signs and symptoms of biopsy-proven human myocarditis (Table 2).

Myocarditis varies with a broad spectrum of symptoms ranging from asymptomatic courses to manifestations with signs of myocardial infarction to life threatening cardiogenic shock and ventricular arrhythmias [11]. However, its three common clinical presentation are chest pain mimicking MI, ventricular arrhythmias and HF due to a new onset of DCM. Myocarditis affects individuals of all ages but it is most frequent in young adults. The diversity of clinical presentation in the course of the disease makes diagnosis based on symptoms difficult and thus requires a high level of suspicion early in the course of the disease and the utility of appropriate tests to identify its cause [9,11]. When myocarditis is suspected, the ESC recommends the exclusion of CAD and other known cardiovascular diseases such as hypertension and extra cardiac non-inflammatory diseases capable of causing the clinical presentation. It is uncommon for patients with other cardiovascular disorders such as CAD, cardiomyopathy and hypertensive heart disease to present with clinical deterioration caused by myocarditis. If symptoms are unclear or inconclusive, endomyocardial biopsy (EMB) may be considered to confirm myocarditis. Myocarditis could be an incidental finding in autopsy studies of non-cardiac deaths or from myocardial samples obtained for clinical reasons unrelated to myocarditis such as after valve surgery or explanted hearts from patients who received inotropic drugs. In such scenario, the significance of inflammation should be interpreted with caution [11].

**Diagnosis**

**Diagnostic criteria**

Definitive diagnosis of myocarditis with HF poses significant challenges. No population-based epidemiological study has comprehensively documented the range of clinical manifestations of acute or chronic myocarditis likely because of varied modes of clinical presentation and the lack of reliable non-invasive cardiac imaging tests reduces the yield of conclusive diagnostic or prognostic value [6]. Because of its varied mode of presentation and the lack of specific features, diagnosis of myocarditis requires a high level of clinical suspicion and integrated evaluation of clinical and instrumental investigations including biomarkers and virus serology tests, ECG, and cardiac imaging tests: echocardiography and cardiac magnetic resonance (CMR) to identify suspected cases of myocarditis HF while EMB confirms diagnosis. The 2013 ESC pericardial and myocardial guidelines proposed diagnostic criteria for myocarditis (Table 3).

**Diagnostic tests**

Biomarkers and virus serology: Biomarkers such as troponins or creatine kinase are non-specific but are useful in raising clinical suspicion of myocarditis [67,68]. In acute myocarditis, serum levels of troponins I and T are higher compared to creatine kinase myocardial band fraction [69]. Non-specific inflammatory markers such as leukocytes and C-reactive protein may also be elevated in acute myocarditis [68,69] but normal values do not exclude acute myocardial inflammatory process [70]. The ESC recommends testing for troponins and C-reactive proteins in all patients suspected with myocarditis [11]. The use of virus serology in patients suspected with myocarditis remains unproven. Comparing nested PCR in EMB, only 4% of patients with clinically suspected myocarditis had serological evidence of the same viral infection [70]. The ESC does not recommend the utility of virus serology testing in patients suspected with myocarditis [11]. It has limited diagnostic value since most virus involved in the pathogenesis of myocarditis are highly prevalent in the population and most patients referred for diagnosis from a few week to months after acute phase of viral myocarditis has already resolved [9]. The interpretation of antibodies (cardiac and disease-specific for myocarditis/ DCM) assays is complicated by reactivation or reinfection but may be useful autoimmune biomarkers for identifying at risk relatives and patients

![Table 2. Clinical manifestations of biopsy-proven human myocarditis](image)

<table>
<thead>
<tr>
<th>Course of Disease</th>
<th>Common Clinical Signs and Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Acute Coronary Syndrome-like</td>
<td>Acute chest pain: frequently starting 1-4 weeks post respiratory or gastrointestinal infection; frequently associated with severe and recurrent symptoms; in the absence of angiographic CAD evidence.</td>
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<td>ST/T wave changes: ST-segment elevation/depression; T-wave inversion</td>
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<td></td>
<td>With/without normal global or regional LV/RV dysfunction on cardiac imaging</td>
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<td></td>
<td>With/without increased TnI/Tnl mimicking acute MI</td>
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<tr>
<td>New onset or worsening HF without CAD and other known causes</td>
<td>New onset/progressive HF (2 weeks- 3 months): dyspnea, peripheral edema, chest discomfort, fatigue</td>
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<td></td>
<td>Systolic/diastolic dysfunction with/without increased wall thickness, dilated LV/RV on cardiac imaging</td>
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<tr>
<td></td>
<td>Non-specific ECG signs: BBB, AV-block or ventricular arrhythmias</td>
</tr>
<tr>
<td>Chronic HF without CAD and other known causes</td>
<td>Fatigue, palpitations, dyspnea, atypical chest pains, arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Systolic/diastolic dysfunction on cardiac imaging suggesting DCM or non-ischemic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Non-specific ECG signs: BBB, AV-block or ventricular arrhythmias</td>
</tr>
<tr>
<td>Life-threatening condition without CAD and other known causes</td>
<td>Life threatening arrhythmias and aborted SCD;</td>
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<tr>
<td></td>
<td>Cardiogenic shock</td>
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<td></td>
<td>LV dysfunction.</td>
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</table>

BBB: Bundle branch block; CAD: Coronary Artery Disease; DCM: Dilated Cardiomyopathy; ECG: Electrocardiogram; HF: Heart Failure; LV: Left Ventricle; MI: Myocardial Infarction; RV: Right Ventricle; SCD: Sudden Cardiac Death. A clinically suspected case of myocarditis should meet the following criteria: ≥ 1 clinical presentation and ≥ 1 diagnostic criteria in the absence of (a) angiographically detected CAD (coronary stenosis ≥ 50%); (b) known pre-existing cardiovascular disease or extra-cardia causes that could explain clinical presentation (valvular heart disease, congenital heart disease, hyperthyroidism); Suspicion increases with higher number of fulfilled criteria. If the patient is asymptomatic, ≥ 2 criteria should be fulfilled. Adapted from European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 2013, p. 2642 [11]
who in the absence of active infection of myocardium would benefit from immunosuppression and/or immunomodulation [9,11].

Electrocardiogram: The 2013 ESC pericardial and myocardial guidelines recommend ECG tests in all patients suspected with myocarditis. ECG is usually abnormal in myocarditis but the findings are both non-specific and non-sensitive [21,71,72]. Some ECG abnormalities are more suggestive of myocarditis than others are. ST/T segment elevation in myocarditis is concave (but convex in MI) and diffuse without reciprocal changes. AV-block in mild ventricular dilatation could result from various causes including laminopathies but may suggest Lyme disease, cardiac sarcoidosis or GCM. ECG abnormalities have also been reported to have prognostic value in patients with myocarditis. QRS prolongation is an independent predictor of survival while Q-waves and repolarization abnormalities are unrelated to outcome or immunohistological features of inflammation [72].

Echocardiography: Echocardiography lacks pathognomonic features for diagnosis of myocarditis. However, it allows the assessment of cardiac chamber sizes and wall thickness as well as systolic and diastolic function in patients suspected with myocarditis. It is an important non-invasive imaging tool to exclude other causes of HF such as valvular heart disease or other cardiomyopathies such as hypertrophic or restrictive. Echocardiographic assessment is usually recommended before EMB procedure to rule out pericardial effusion and intra-cavity thrombi, which occur in up to 25% of patients [10]. In addition, evaluation of different echocardiographic parameters has prognostic relevance in myocarditis patients. In fulminant myocarditis, patients have normal cardiac chamber sizes with increased septal thickness in the setting of acute myocardial edema while in acute myocarditis patients have marked LV dilatation and normal wall thickness [73]. The role of other echocardiographic techniques such as tissue Doppler or strain rate in the diagnosis of myocarditis have not been determined. The 2012 ESC guidelines recommends all patients with clinically suspected myocarditis should undergo standard trans-thoracic echocardiogram at presentation and during hospitalization in the case of worsening hemodynamics [11].

Cardiac magnetic resonance: Cardiac magnetic resonance (CMR) imaging is fast emerging as a valuable non-invasive imaging tool for tissue characterization of the myocardium to support the diagnosis of myocarditis. The timing of imaging in suspected patients usually depends on local availability and expertise but CMR is recommended in stable patients before EMB. CMR is not recommended in life-threatening presentation where EMB is urgently indicated. Based on additional clinical information. To improve diagnostic accuracy, the use of large panel of monoclonal and polyclonal antibodies is mandatory to identify and characterize inflammatory infiltrates [53,54]. To exclude systemic infection, peripheral blood should evaluated with EMB viral quantification and replication [77]. Although its prognostic value has not been determined, CMR may be repeated is necessary to monitor response to etiology-specific therapy [77].

**Meta-analysis of diagnosis methods**

Myocarditis is an inflammatory disease of the myocardium and an importance cause of acute HF, SCD and DCM in young adults. Its diagnosis is complicated by great variability in clinical presentation and evolution, and the lack of reliable cardiac imaging tests [11,78]. While REM remains the gold standard for a confirmatory diagnosis, its invasive nature and the risk of severe complications has limited its use in clinical settings [78]. Conversely, CMR imaging is gaining widespread use for assessing clinically suspected myocarditis due to its ability to detect myocardial inflammation, myocardial edema and fibrosis [79]. The Lake Louise Consensus Criteria suggests the combined utility of two or three CMR techniques (T1-weighted, T2-weighted and/or LGE) improves diagnostic accuracy [74]. The present meta-analysis seeks to compare diagnostic performance of CMR (sensitivity, specificity and accuracy) based on the Lake Louise Consensus Criteria in reference to EMB procedure. Search strategy, study selection, data extraction and analysis were performed based on PRISMA guidelines for systematic reviews and meta-analysis [80].

Study search and inclusion criteria: The search for studies on CMR and EMB diagnosis of myocarditis HF was conducted on online databases PubMed, EMBASE and Cochrane Central Register of Controlled Trials. The search strategy was based on a combination of the following key terms "cardiac magnetic resonance imaging" AND "myocarditis" OR "inflammatory cardiomyopathy" OR "inflammation

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**Table 3. The ESC diagnostic criteria for myocarditis heart failure**

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Outcomes/Findings</th>
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<tbody>
<tr>
<td>I. ECG/Holter/Stress Test</td>
<td>I-II degree AV-block or BBB, ST/T wave change, sinus arrest, ventricular tachycardia/ fibrillation, AF, reduced R wave height, wide QRS complex, abnormal Q waves, frequent premature beats, supraventricular tachycardia</td>
</tr>
<tr>
<td>II. Myocardioctylosis markers</td>
<td>Elevated Tei/Ti/Tn</td>
</tr>
<tr>
<td>III. Imaging</td>
<td>Unexplained LV/RV abnormalities; regional wall motion/global systolic dysfunction with/without ventricular dilatation, with/without increased wall thickness, with/without pericardial effusion, with/without endocarditis thrombs</td>
</tr>
<tr>
<td>IV. Tissue characterization by CMR</td>
<td>Edema and/or LGE classical myocardial pattern</td>
</tr>
</tbody>
</table>

**AV-Block: Atrioventricular block; BBB: Bundle branch block; CMR: Cardiac Magnetic Resonance; ECG: Electrocardiogram; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; RV: Right Ventricle. Adapted from European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 2013, p. 2643 [11]**

<table>
<thead>
<tr>
<th>Table 4. Proposed CMR diagnostic criteria for myocarditis heart failure</th>
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<tbody>
<tr>
<td><strong>In patients with clinical suspicion of myocarditis</strong>, CMR findings are consistent with myocardial inflammation if at least two the following criteria are present:</td>
</tr>
<tr>
<td>1. Regional or global myocardial signal intensity in T2-weighted images;</td>
</tr>
<tr>
<td>2. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images;</td>
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<tr>
<td>3. There is at least one focal lesion with non-ischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (LGE);</td>
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<tr>
<td><strong>A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present</strong></td>
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<tr>
<th>A repeat CMR study 1-2 weeks after the initial CMR study is recommended if</th>
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<tbody>
<tr>
<td>1. None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation</td>
</tr>
<tr>
<td>2. One of the criteria is present</td>
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<tr>
<th>The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis</th>
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<tr>
<td>a: The clinical suspicion for active myocarditis should be based on the criteria listed in Table 2;</td>
</tr>
<tr>
<td>b: Global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥2.0. If the edema is more subendocardial or transmural in combination with a co-localized ischemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported</td>
</tr>
<tr>
<td>c: A global SI enhancement ratio of myocardium over skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45% is consistent with myocarditis.</td>
</tr>
<tr>
<td>d: Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the sub-epicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is co-localized with a transmural regional edema, acute myocardial infarction is more likely and should be reported</td>
</tr>
</tbody>
</table>

Adapted from International Consensus Group on CMR in Myocarditis [74]

dilated cardiomyopathy" AND "endomyocardial biopsy". Additional studies were obtained from manual search of bibliographies of included studies and review articles. The search was restricted to human studies. There was no restriction on publication language and time.

Studies were eligible for inclusion if they met the following criteria: (a) were randomized controlled prospective or retrospective clinical trials; (b) recruited patients suspected with myocarditis or inflammatory DCM with reduced ejection fraction; (c) evaluated diagnostic performance of CMR using EMB as reference standard; and (d) provided sufficient data to compared diagnostic performance of CMR against EMB. Case series and studies that did not use original data such as duplicate studies, review articles, and editorials were excluded. All published articles investigating diagnostic performance of CMR with reference EMB were identified. Studies the categorized patients in groups, each group was analyzed separately.

Two reviewers screened titles and abstract for potential studies, and in the second step, all potentially suitable articles were reviewed for final eligibility. Duplicates were identified and excluded. Full-text of all included studies were obtained and two investigators independently assessed study eligibility and extracted data. The following details were recorded from each study: study characteristics (first author, publication year, and study design), patient characteristics (number, mean age and proportion of male) and diagnostic performance (sensitivity, specificity and accuracy) as summarized in Table 5.

Study characteristics and outcomes: The initial online search and screening of bibliographies and review articles yielded 271 articles. After screening titles and abstracts, 22 studies were selected for full text screening. Finally, six studies meeting the eligibility criteria were included in this meta-analysis [81-86]. The total number of patients enrolled in the six studies were 474. The patients were relatively young (mean age = 47 years) with a majority being of the male gender (72%). The performance of CMR in the diagnosis of myocarditis HF was assessed using three CMR techniques in reference to EMB: T1-W global relative enhancement (gRE), T2-W edema ratio of the myocardium (ER), and late gadolinium enhancement (LGE) in contrast CMR imaging and Lake Louise Criteria (LLC). One study grouped patients into two (acute and chronic myocarditis) [86] and another into three based on myocarditis pattern (infarct-like, cardiomyopathic and arrhythmic patterns) [84]. Each group was analyzed separately. The most common diagnosis of EMB was myocarditis (36.0% [83], 52.0% [85], 58.0% [81], 62.8% [82]. Weighted mean revealed sensitivity, specificity and accuracy for LGE (48%, 72% and 61%), gRE (68%, 65% and 64%), ER (69%, 72% and 72%) and LLC (69%, 56% and 67%). Our findings suggest that CMR imaging based on LLC and its three components (LGE, gRE and ER) are moderately accurate in the diagnosis of myocarditis HF in clinically suspected patients. The findings also suggests EMB remains the gold standard for confirmatory diagnosis of myocarditis and a need to develop newer parameters or imaging technique to improve CMR diagnostic performance.

Discussion: Despite various imaging modalities available today, diagnostics of myocarditis HF is a demanding task and remains diagnosis of exclusion. The ESC recommends EMB with immunohistochemistry and PCR (for viral genomes) for diagnosing myocarditis as well as providing additional insight about underlying etiology and pathogenic mechanisms [11,84,87]. However, EMB is invasive, is associated with increased risk of complication and is only considered first choice method only in specialized health centers with the experience and expertise in performing the procedure [87]. For these reasons, CMR imaging based on the LLC is becoming the criterion standard for non-invasive diagnosis of myocarditis. It allows the identification of the hallmarks of myocardial inflammation (edema, fibrosis, and hyperemia), and is able to characterize tissue and to assess regional and global biventricular function [74]. However, current research evidence on the diagnostic performance of CMR rely on small-scale studies, which have inconsistent findings. In the present meta-analysis, CMR has a moderate diagnostic performance relative to EMB in patients with a clinical suspicion of myocarditis.

Moderate accuracy of CMR parameters as defined by the LLC have also been described elsewhere. The three CMRI parameters LGE, gRE and ER investigated in the present study provide surrogate measures for three common histopathological features of myocardial inflammation – myocardial edema, hyperemia and fibrosis, which may have lower sensitivity and specificity for myocarditis compared to other cardiovascular diseases [74,78]. In myocarditis, LGE in contrast CMR imaging, which reflects myocardial necrosis and fibrosis has been shown to be non-specific and non-sensitive because necrosis and fibrosis could also be observed in many other cardiac diseases with myocardial injury and remodeling such as cardiac sarcoidosis and non-ischemic cardiomyopathy [88,89]. In addition, patients with moderate myocarditis have insignificant myocardial necrosis and fibrosis that LGE may not detect [89]. T2-W edema ratio reflects the extent of myocardial edema is also non-specific since it is a feature observed in other cardiac diseases with myocardial interstitial injury [91]. Low signal-to-noise ratio also limits the diagnostic accuracy of ER [92]. Lastly, T1-W gRE
reflect myocardial hyperemia is also non-specific to myocarditis [92]. Signal intensity of skeletal muscle is used for the normalization of the gRE ratio, and in the presence of skeletal muscle disease, gRE may give false negative [93].

Whereas a recent International Consensus Group on Cardiovascular MR in Myocarditis suggests combining at least two CMR parameters improves diagnostic accuracy, the present findings still show moderate diagnostic performance. The findings suggest the need for developing novel CMR parameters and/or imaging techniques to improve the accuracy of non-invasive diagnosis of myocarditis. However, our analysis may be limited with small number of studies and patients as well as significant heterogeneity among individual studies with regard to duration of symptoms, presence of co-morbidities and CMRI protocols used in imaging contributing to heterogeneity.

Clinical management

Ideally, clinical management of strategies for myocarditis HF should target the causal pathophysiology but the effect of a specific etiology-focused therapy has only been confirmed in a few studies on inflammatory heart diseases such as GCM and sarcoidosis. Since patients with myocarditis have a high incidence of impaired LV function, evidence-based HF therapy is strongly recommended to these patients [9]. The primary target of myocarditis treatment are optimal care of arrhythmias and HF, and etiologic agents.

Treatment strategies

Three strategies have been recommended for treating patients diagnosed with myocarditis HF: (a) HF therapy; (b) Immunomodulatory therapy; and (c) Immunosuppressive therapy [11].

Heart failure therapy: Myocarditis patients with hemodynamically unstable HF should receive prompt evidence-based HF medication according to the current ESC HF guidelines [94] in intensive care units with respiratory and mechanical cardio-pulmonary support facilities. Patients with acute or fulminant myocarditis presenting with cardiogenic shock and severe LV or RV dysfunction, mechanical circulatory support device or extracorporeal membrane oxygenation (ECMO) is recommended as a bridge to recovery or cardiac transplantation [95-98]. In patients suspected myocarditis who are asymptomatic or mildly symptomatic based on clinical suspicion criteria (Table 2), hospital admission and clinical monitoring are recommended until the establishment of a definite diagnosis. Monitoring is important since myocarditis can develop rapidly into a cardio-pulmonary emergency (lethal arrhythmias or severe heart block) despite preserved systolic function [95]. Exercise testing is contraindicated due to increased risk of arrhythmias [11].

Recommendation medications for myocarditis patients with hemodynamically stable HF are diuretics, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). The 2012 ESC HF guidelines recommend consideration of additional aldosterone antagonist therapy for patients with persistent HF symptoms despite optimal clinical management [99]. However, weaning procedures of HF therapy after recovery of ventricular function remain undefined. Non-steroidal anti-inflammatory drugs are efficacious in acute pericarditis patients but experimental myocarditis animal models document increased risk of mortality [59,100] while clinical data in humans are inconclusive [11]. No recommendations for specific therapy for myocarditis patients with arrhythmias but strategies adopted should be consistent with the current ESC HF guidelines [94]. Temporary pacing may be considered in patients with complete AV-block. The utility of implanted cardioverter defibrillator remains controversial since myocarditis may heal completely. However, wearable cardioverter defibrillator in myocarditis patients with severe ventricular arrhythmias (AF or ventricular tachycardia) could solve the transient nature of myocarditis [101]. In the acute phase of myocarditis, in addition to medication, patients should avoid physical activity until the disease has completely healed [102-103]. Despite age, gender, severity of symptoms and therapeutic regime, athletes should be excluded from sporting activity until the resolution of clinical presentation and follow-up clinical indication [103].

Immunomodulatory therapy: Immunomodulatory therapy for patients with myocarditis HF may include antiviral, intravenous immunoglobulin and immunoadsorption therapies [11]. The rationale for considering antiviral therapy is based on the knowledge that the most common causes of myocarditis are secondary to viral infection [9]. However, at present, there are no proven antiviral therapies for the treatment of enteroviral infections. Vaccines are a promising option in the future. Acyclovir, gancyclovir, and valacyclovir may be considered in treatment of enteroviral infections. Vaccines are a promising option in the future. Acyclovir, gancyclovir, and valacyclovir may be considered in herpes virus infection but its efficacy is unproven in myocarditis [104]. Primary evidence on interferon-beta treatment suggests it eliminates enteroviral and adenoviral infections in patients with impaired LV function as well as improves in New York Heart Association (NYHA) functional class [105]. If the use of specific antiviral therapies is considered, infectious disease specialists should be involved [11].

Intravenous immunoglobulin (IVIG) in high doses have been shown to modulate immune and inflammatory response [11]. It has been used in a number of systemic autoimmune disorders and has been associated with improved LV ejection fraction in chronic overt HF but ineffective in recent onset of DCM 15% with biopsy-proven myocarditis of unspecified cause [106]. Since IVIG has no adverse side effects, it may be considered in patients with viral and autoimmune myocarditis.
Immunoadsorption (IA) targets to eliminate anti-cardiac antibodies against various cardiac cell proteins, which have been found in patients with DCM and myocarditis. The removal of circulating antibodies by IA in DCM patients has been shown to improve cardiac function [107] and humoral markers of HF severity such as exercise capacity and natriuretic peptides [108,109]. IA has also been associated with improvements in hemodynamic parameters such as stroke volume index and systemic vascular resistance [110] and decreased myocardial inflammation [107]. The current evidence suggests IA may be a promising treatment for patients with autoimmune myocarditis HF or DCM. However, therapeutic value of IA in myocarditis has not been determined but ongoing small-scale randomized controlled trials in Europe exploring the use of IA and its value in myocarditis [11].

Immunosuppressive therapy: Immunosuppressive therapy (cyclosporine, prednisolone, azathioprine) in acute myocarditis have had inconclusive findings. In patients with chronic DCM, azathioprine and prednisolone improved LV function and NYHA functional class [57,110]. In the Immunosuppressive Therapy in Patients with Virus Negative Inflammatory Cardiomyopathy (TIMIC) study, prednisone and azathioprine caused significant improvement in LV ejection fraction and a decrease LV dimensions [111]. The ESC [11] recommends immunosuppressive therapy should only be started after excluding active infection by PCR on EMB. Immunosuppression may also be considered in proven autoimmune (infection negative) forms of myocarditis HF with no contraindications including GCM, cardiac sarcoidosis and myocarditis associated with known extra-cardiac autoimmune disease. Steroid therapy is indicated in cardiac sarcoidosis with LV dysfunction and/or arrhythmias and in toxic myocarditis with HF and/or arrhythmias. Immunosuppression requires follow-up EMB to guide the intensity and length therapy [11].

Meta-analysis of immunomodulatory and immunosuppressive therapies

Myocarditis HF lacks curative therapy. Current clinical management strategies largely focus on relief of HF symptoms and concomitant adverse events using traditional HF therapies. Since deleterious inflammatory reaction to viral infection induces myocardial dysfunction, therapies targeting immunomodulation may have potentially beneficial outcomes [106-109]. In addition, long-term consequences of myocarditis have been associated with the activation of cellular and humoral auto-immunity suggesting potential benefits of immunosuppressive therapy [17,110-111]. However, the current research evidence on therapeutic value of immunomodulation and immunosuppression therapies for patients with myocarditis are inconclusive. This meta-analysis pools together data from relevant clinical trials to determine clinical benefits of using immunomodulatory and immunosuppressive therapies in patients with myocarditis HF.

Study search and inclusion criteria: Studies investigating clinical benefits of immunomodulatory or immunosuppressive therapies on patients with myocarditis HF were searched from online databases PubMed, EMBASE and Cochrane Central Register of Controlled Trials. The search strategy was based on a combination of the following key search terms: “myocarditis” OR “inflammatory cardiomyopathy” AND “immunomodulatory” OR “immunosuppressive”. Bibliographies of included studies and review articles were also searched to identify additional articles missed by the online search. Eligibility criteria for inclusion were the studies; (a) enrolled patients with myocarditis or inflammatory cardiomyopathy; (b) randomized or quasi-randomized patients into treatment or placebo groups; (c) compared immunomodulatory or immunosuppressive with placebo or conventional therapies; and (d) reported effect on cardiac function.

Two reviewers independently assessed the studies for eligibility and inclusion and disagreements resolved through consensus. The following details were recorded from each study included: first author, publication year, number of patients enrolled, mean age and proportion of male patients, type of therapy and outcomes of therapy (Table 6). The primary efficacy outcomes was LVEF measured by echocardiography or scintigraphy, NYHA and viral clearance and resolution of inflammatory filtrate. Continuous data was reported using mean and standard deviation. Treatment effects for dichotomous outcomes were expressed as odds ratio with 95% CI. Pooled effect was calculated using fixed effect model and random effect model. Statistical significance was defined as p < 0.01 or I² > 25%.

Study characteristics and outcomes: The initial search identified 206 potential studies. After title, abstract and full-text-screening against the inclusion criteria, six studies were included in this meta-analysis [20,57,111-114]. The combined patient population was 471 with biopsy-proved myocarditis or inflammatory cardiomyopathy with demonstrated LV dysfunction randomized into treatment group (n = 235) and control or placebo group (n = 236). Patients were relatively young (mean age = 42 years) with a predominant male population (68%). The main drugs investigated were prednisone, azathioprine or cyclosporine, and interferon-alpha or thymomodulin. The main clinical endpoints studied were improvement of LVEF ≥ 5% and cases adverse clinical endpoints defined as death or cardiac transplantation. Our pooled analysis reveals that treatment of myocarditis HF using

Table 6. Characteristics of randomized trials on immunosuppressive therapy

<table>
<thead>
<tr>
<th>1st Author [Ref#]</th>
<th>Year</th>
<th>Patient Size</th>
<th>Age (yrs.)</th>
<th>Male (%)</th>
<th>Drug</th>
<th>Improved LVEF (%)</th>
<th>Died/HTx (%)</th>
<th>FUP (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latham et al.</td>
<td>1989</td>
<td>12/40</td>
<td>41/81</td>
<td></td>
<td>Prednisone</td>
<td>NR</td>
<td>NR</td>
<td>11/24</td>
</tr>
<tr>
<td>Parrillo et al.</td>
<td>1989</td>
<td>49/52</td>
<td>43/45</td>
<td>NR</td>
<td>Prednisone</td>
<td>5/9</td>
<td>9/5</td>
<td>15</td>
</tr>
<tr>
<td>Mason et al.</td>
<td>1995</td>
<td>64/47</td>
<td>43/58</td>
<td></td>
<td>Azathioprine/ cyclosporine* prednisone</td>
<td>54/35</td>
<td>NR</td>
<td>23</td>
</tr>
<tr>
<td>Miric et al.</td>
<td>1996</td>
<td>26/12</td>
<td>19/56</td>
<td></td>
<td>Interferon-alpha or thymomodulin</td>
<td>21/8</td>
<td>3/2</td>
<td>24</td>
</tr>
<tr>
<td>Wojnicz et al.</td>
<td>2001</td>
<td>41/33</td>
<td>39/82</td>
<td></td>
<td>Azathioprine + prednisone</td>
<td>24/11</td>
<td>8/8</td>
<td>24</td>
</tr>
<tr>
<td>Frustaci et al.</td>
<td>2009</td>
<td>43/42</td>
<td>44/60</td>
<td></td>
<td>Azathioprine + prednisone</td>
<td>38/7</td>
<td>0/2</td>
<td>24</td>
</tr>
</tbody>
</table>
immunosuppressive therapy compared to conventional HF therapies has a short-term benefit in improving LVEF (OR: 3.2, 95% CI: 2.09-5.05, p<0.001, I^2=65.8%) (Figure 2) but there was no evidence of significant effect on protection against all-cause death and/or cardiac transplantation (OR: 1.7, 95% CI: 0.9-3.1, p=0.08, I^2=69.7%) (Figure 3).

Discussion

Current recommended treatment of myocarditis HF and inflammatory DCM largely focuses on supportive care with evidence-based and guideline-directed treatment of HF and arrhythmias [11,99]. Although the suppression of autoimmune response in chronic myocarditis has been considered potentially beneficial, limited availability of RCTs testing this hypothesis reflects insufficient evidence for therapeutic benefits of immunosuppressive therapy in these patients. In the present meta-analysis, we identified six studies assessing the effect of immunosuppressive or immunomodulatory therapy but individual studied investigated different treatment strategies (immunosuppressive single or combination therapy) thus analysis of pooled treatment effect was not feasible. We instead chose to investigate treatment effect on surrogate endpoints (improvement in LVEF function defined by echocardiography, and death or cardiac transplantation) in patients with EMB-proven myocarditis HF.

In our analysis, there is no evidence that immunosuppressive therapy for myocarditis patients with HF will provide a greater protective effect against death or cardiac transplantation compared to the conventional HF therapy. Although in the short-term, immunosuppressive therapy may induce a mild improvement in LV function (mildly increased LVEF), the effect is not sustained in the long-term. The findings support that cardiac transplantation may be the only long-term treatment strategy that can prolong survival in patients with myocarditis HF. Previous meta-analysis on immunomodulation therapy [116] and immunosuppressive therapy [117] provide similar findings, reporting that immunomodulatory and immunosuppressive therapies have a non-significant effect on cardiac function, all cause death and the need for cardiac transplantation.

However, for patients with histologically proven infection-negative myocarditis, a combination of immunosuppressive therapies might be clinically beneficial [117]. In a single-center study, Frustaci et al. [114] suggested beneficial effect of combining steroid and azathioprine therapy in patients with virus-negative myocarditis. The ESC also recommends immunosuppressive therapy on infection negative patients and follow-up EMB to guide treatment intensity and duration [11]. However, additional clinical trials with long-term follow-up and consideration of treatment intensity and duration are needed to determine therapeutic benefits of immunomodulatory and immunosuppressive therapies for high-risk myocarditis patients presenting with major clinical syndromes (severe HF and/or life threatening arrhythmias) who are refractory to conventional HF therapies.

Conclusion

Myocardial heart failure a cardiac syndrome resulting from acute or chronic inflammation of the myocardium produced by infectious agents or drugs and toxins with LV dilatation and depressed ejection fraction. It is more predominant among young adults. It has a predominant viral etiology and less frequently bacterial, fungi and parasites, and non-infectious causes such as systemic autoimmune responses and drug-induced hypersensitivity. Pathophysiological mechanisms are triphasic. In the initial acute phase, viral infection and replication induces innate immune response. In the subacute phase, myocardial damage induces autoantibodies and autoimmune cells through epitope spreading or molecular mimicry. In the chronic phase, low-grade viral persistence and sustained inflammation induces myocardial remodeling leading to ventricular dilatation and contractile dysfunction and ultimately heart failure. It has varied modes of clinical manifestations in its clinical course ranging from asymptomatic and non-specific systemic symptoms to life threatening cardiogenic shock and ventricular arrhythmias making diagnosis-based on symptoms impossible. Confirmatory diagnosis is challenging because of diversity of symptoms and limited utility of endomyocardial biopsy considered the gold standard for diagnosing myocarditis HF. Integrated evaluation of clinical and instrumental non-invasive tests (biomarkers and virus serology, ECG, echocardiography and cardiac magnetic resonance imaging is fundamental to identify suspected myocarditis HF. However, histologic and immunohistochemical analysis of myocardial tissue samples obtained with an endomyocardial biopsy established diagnosis. Clinical management targets treating HF using conventional HF therapies and the underlying etiology using immunomodulatory or immunosuppressive therapy.

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