

# Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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In this position statement of the ESC Working Group on Myocardial and Pericardial Diseases an expert consensus group reviews the current knowledge on clinical presentation, diagnosis and treatment of myocarditis, and proposes new diagnostic criteria for clinically suspected myocarditis and its distinct biopsy-proven pathogenetic forms. The aims are to bridge the gap between clinical and tissue-based diagnosis, to improve management and provide a common reference point for future registries and multicentre randomised controlled trials of aetiology-driven treatment in inflammatory heart muscle disease.

**Keywords** Myocarditis • Cardiomyopathy • Diagnosis • Therapy

## Introduction

Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentations.<sup>1–3</sup> The actual incidence of myocarditis is also difficult to determine as endomyocardial biopsy (EMB), the diagnostic gold standard,<sup>1–3</sup> is used infrequently.<sup>2,3</sup> Studies addressing the issue of sudden cardiac death in young people report a highly variable autopsy

prevalence of myocarditis, ranging from 2 to 42% of cases.<sup>4,5</sup> Similarly, biopsy-proven myocarditis is reported in 9–16% of adult patients with unexplained non-ischaemic dilated cardiomyopathy (DCM)<sup>6,7</sup> and in 46% of children with an identified cause of DCM.<sup>8</sup> In patients presenting with mild symptoms and minimal ventricular dysfunction, myocarditis often resolves spontaneously without specific treatment.<sup>9</sup> However, in up to 30% of cases, biopsy-proven myocarditis can progress to

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DCM and is associated with a poor prognosis.<sup>1–3,7–9</sup> Prognosis in myocarditis patients also varies according to the underlying aetiology.<sup>9</sup> The treatment of many forms of myocarditis is symptomatic,<sup>10</sup> but immunohistochemical<sup>1–3,9,10,11–15</sup> and molecular biological analysis of EMB<sup>16</sup> as well as autoantibody serum testing is important to identify those patients in whom specific therapy is appropriate.<sup>9,17</sup>

In this Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, an expert consensus group has reviewed the current literature on clinical presentation, diagnosis, and treatment of myocarditis and propose new diagnostic criteria for clinically suspected myocarditis. The present article is an opinion statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.

## Definitions

In this document, we recommend use of existing definitions of myocarditis and inflammatory cardiomyopathy (Box 1), but acknowledge that there is some confusion about the terms DCM and inflammatory cardiomyopathy. Dilated cardiomyopathy is a clinical diagnosis based on morphological and functional characterization of the left ventricle; inflammatory cardiomyopathy is both a histological and functional diagnosis characterized by myocarditis in association with systolic and/or diastolic cardiac dysfunction; thus inflammatory cardiomyopathy and DCM are not mutually exclusive.

### Definitions

Myocarditis (WHO /ISFC<sup>1</sup>):

*Inflammatory disease of the myocardium diagnosed by established histological\*, immunological and immunohistochemical criteria\*\*.*

\*N.B. established histological Dallas criteria<sup>12</sup> defined as follows:

*'histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin'<sup>12</sup>.*

\*\*N.B. unspecified immunohistochemical criteria<sup>1</sup>, we propose an abnormal inflammatory infiltrate to be defined as follows:

*' $\geq 14$  leucocytes/mm<sup>2</sup> including up to 4 monocytes/mm<sup>2</sup> with the presence of CD 3 positive T-lymphocytes  $\geq 7$  cells/mm<sup>2</sup>.'<sup>15,18,19</sup>*

Inflammatory Cardiomyopathy (WHO /ISFC<sup>1</sup>):

*Myocarditis in association with cardiac dysfunction.*

N.B. Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.<sup>1</sup>

Dilated Cardiomyopathy (ESC<sup>13</sup>; WHO /ISFC<sup>1</sup>):

*DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.*

N.B. DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.<sup>1</sup>

The histological diagnosis of myocarditis includes different forms, classified according to the type of inflammatory cell infiltrate: lymphocytic, eosinophilic, polymorphic, giant cell myocarditis, and cardiac sarcoidosis.<sup>2,4,12</sup> The task group also recommends the following criteria for subsets of myocarditis or inflammatory cardiomyopathy.<sup>1,2,9,13,14,16–19</sup>

## Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (Table 1).

## Autoimmune myocarditis

Histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies (aabs) (Table 2).

N.B. There are autoimmune diseases (e.g. Hashimoto's thyroiditis) where aabs are mainly biomarkers, autoantibody-mediated forms (e.g. Graves' disease), in which aabs are pathogenic, and cell-mediated autoimmune diseases, which are negative for aabs. In all cases, autoimmune diseases are negative for infectious agents.

## Viral and immune myocarditis

Histological myocarditis with positive viral PCR and positive cardiac aabs (Table 2).

N.B. A follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac aabs, e.g. post-infectious autoimmune disease.

## Aetiology of myocarditis

Although the aetiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic diseases, drugs, and toxins can cause the disease (Table 1).<sup>1–3,11,16,21–24</sup> Some causes of myocarditis are now largely historical or occur in very specific scenarios such as sepsis or in immunocompromised patients. Molecular techniques, mainly (reverse transcriptase)(RT)-PCR amplification,<sup>9,18,19,22,24–34</sup> suggest that viral infections are the most important cause of myocarditis in North America and Europe with genomes of enterovirus, adenovirus, influenza viruses, human herpes virus-6 (HHV-6), Epstein-Barr-virus, cytomegalovirus, hepatitis C virus, and parvovirus B19 reported in the myocardium of patients with myocarditis and DCM. Lymphocytic and giant cell myocarditis are presumed idiopathic or autoimmune if no viruses are identified in EMB and other known causes are excluded (Figure 1).<sup>17</sup> Similarly, the diagnosis of idiopathic granulomatous myocarditis (cardiac sarcoidosis) requires negative stains for microorganisms.<sup>2</sup> Autoimmune myocarditis may occur with exclusive cardiac involvement or in the context of autoimmune disorders with extra-cardiac manifestations,<sup>9,11,17</sup> most frequently in sarcoidosis (Figure 1), hypereosinophilic syndrome, scleroderma, and systemic lupus erythematosus.

## Pathogenesis

In human myocarditis, there is evidence for viral and autoimmune mechanisms, acting in individuals with or without a genetic predisposition (familial or sporadic cases, respectively).<sup>14,15,18,35–103</sup> Murine studies of viral myocarditis<sup>23,104–107</sup> are based mostly on Coxsackievirus B3-infected animals, which exhibit strain-specific susceptibility. Enteroviruses that preferentially enter cardiomyocytes via specific receptors cause severe cytopathic effects due to virus replication in the first 2 weeks post-infection. As a consequence, a humoral and cellular immune response, mainly consisting of macrophages and CD4+ and CD8+ T- lymphocytes, is initiated in resistant

**Table 1** Causes of myocarditis/inflammatory cardiomyopathy

1. Infectious myocarditis	
Bacterial	<i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Pneumococcus</i> , <i>Meningococcus</i> , <i>Gonococcus</i> , <i>Salmonella</i> , <i>Corynebacterium diphtheriae</i> , <i>Haemophilus influenzae</i> , <i>Mycobacterium</i> (tuberculosis), <i>Mycoplasma pneumoniae</i> , <i>Brucella</i>
Spirochaetal	<i>Borrelia</i> (Lyme disease), <i>Leptospira</i> (Weil disease)
Fungal	<i>Aspergillus</i> , <i>Actinomyces</i> , <i>Blastomyces</i> , <i>Candida</i> , <i>Coccidioides</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Mucormycoses</i> , <i>Nocardia</i> , <i>Sporothrix</i>
Protozoal	<i>Trypanosoma cruzi</i> , <i>Toxoplasma gondii</i> , <i>Entamoeba</i> , <i>Leishmania</i>
Parasitic	<i>Trichinella spiralis</i> , <i>Echinococcus granulosus</i> , <i>Taenia solium</i>
Rickettsial	<i>Coxiella burnetii</i> (Q fever), <i>R. rickettsii</i> (Rocky Mountain spotted fever), <i>R. tsutsugamuschi</i>
Viral	RNA viruses: Cocksackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
2. Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)
3. Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)
Miscellaneous	Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Phaeochromocytoma, vitamins: beri-beri
Physical agents	Radiation, electric shock

animals (C57BL/6 mice, Sv129 mice) and leads to the elimination of the infectious agent within 2 weeks following infection. In susceptible mouse strains (e.g. A/J, ABY/SnJ, ASW/SnJ, ACA/SnJ, SWR/J, Balb/c), viral RNA and inflammation persist in the heart for several weeks.<sup>104–105</sup> There is evidence that in these susceptible mice strains, the ongoing infection and inflammation trigger autoimmune reactions in the heart, most likely as a result of myocyte necrosis and subsequent release of self-antigens previously hidden to the immune system (Figure 2).<sup>108</sup> The same genetically predisposed strains of animals develop autoimmune lymphocytic or giant cell myocarditis and later DCM after immunization with cardiac autoantigens (e.g. cardiac myosin) or spontaneously. In common with other autoimmune diseases such as Type 1 diabetes, major histocompatibility complex (MHC) and non-MHC genes appear to be responsible for the predisposition to murine myocarditis.<sup>17,108–115</sup>

It is likely that genetic predisposition is also important for the development of viral<sup>116</sup> and/or autoimmune myocarditis and its progression to DCM in humans.<sup>35–36,117</sup> Progression from myocarditis to DCM seems to occur predominantly in patients with histologically confirmed persistent (chronic) inflammation<sup>18</sup> that cannot eliminate the infective microbial agents<sup>32</sup> or have developed pathogenic cardiac autoantibodies directed against myocardial structural, sarcoplasmic, or sarcolemmal proteins. The frequency, cardiac, and disease specificity for such antibodies in myocarditis/DCM are summarized in Table 2.<sup>9,36,37,118,119</sup>

## Clinical presentation

Myocarditis presents in many different ways, ranging from mild symptoms of chest pain and palpitations associated with transient ECG changes to life-threatening cardiogenic shock and ventricular arrhythmia (Table 3). The disease may affect individuals of all ages, although it is most frequent in the young. This diversity of clinical scenarios implies that the diagnosis of myocarditis requires a high level of suspicion early in the course of the disease and the use of appropriate investigations to identify its cause. In all cases of suspected myocarditis, it is mandatory to exclude coronary artery disease and other cardiovascular, e.g. hypertension, or extra-cardiac non-inflammatory diseases that could explain the clinical presentation. Rarely patients with other cardiovascular disorders such as coronary artery disease, cardiomyopathy, and hypertensive heart disease present with a clinical deterioration caused by myocarditis that is mistakenly attributed to the natural history of the preexisting disease. If this is strongly suspected by the clinician, further investigation including EMB may be appropriate.

Myocarditis can be an incidental finding in autopsy studies of individuals who died of non-cardiac death or in myocardial samples obtained for clinical reasons unrelated to the clinical suspicion of myocarditis, for example following valve surgery or in explanted hearts taken from patients that have received inotropic drugs. In these circumstances, the significance of myocardial inflammation must be interpreted cautiously in the light of the clinical scenario.

**Table 2** Serum cardiac autoantibodies in autoimmune myocarditis/dilated cardiomyopathy: frequency in myocarditis/dilated cardiomyopathy, other cardiac disease (OCD) and normals

Cardiac autoantibody (Ab)	% aabs positive		%antibody positive		Functional effect/clinical relevance	References
	Myoc	DCM	OCD	Normal		
Muscle-specific ASA, (AFA, IFA, AMLA)	28–59*	9–41*	NT	0–25	Myocytolysis	72,77,57,64
Cardiac-specific						
AHA	41–56* <sup>a</sup>	26–30* <sup>a</sup>	1–4	3	Cardiac- and disease-specific early predictors; predict DCM development in relatives	9 <sup>a</sup> ,50 <sup>a</sup> ,35 <sup>a</sup> , 36 <sup>a</sup> ,118 <sup>a</sup> ,52 <sup>a</sup>
AIDA	17* <sup>a</sup>	16* <sup>a</sup>	2–4	0		
Anti-Beta1-AR	33 NT 73–96* <sup>a</sup> NT	40–51 <sup>^</sup> 35* <sup>a</sup> 29–95* <sup>a</sup> 27–28	13–55 16 8 10	0–13 7 0 0	Negative predictors, pro-apoptotic and other <i>in vitro</i> effects <sup>b</sup>	48,55,61–63,66 <sup>a</sup> ,72,74–76, 78,84,109,88,90,92,93,98
Anti-Beta2-AR	NT NT NT	30–38 <sup>^</sup> 13–14 30–75 <sup>a</sup>	33 37	15 18	Association with idiopathic arrhythmia	53 <sup>^</sup> ,62,69 <sup>a</sup> ,89
Anti-muscarinic acetylcholine receptor-2	11 NT	30–77 <sup>c</sup> 83 <sup>e</sup>	23 <sup>d</sup> –61	8–13	Negative inotropic, muscarinic effects Association with atrial arrhythmia	47 <sup>d</sup> ,48 <sup>c</sup> ,54,58,59,70,74–75,88,94,98
Cardiodepressant (Fy-gamma-receptor 2a)	NT	64			Negative inotropic effects in rat and human myocytes <i>in vitro</i>	56,66 <sup>^</sup> ,85–87,91 <sup>^</sup>
Anti-Ky channel-interacting protein 2, KChIP2.6—ELISA)	NT	14 <sup>^</sup>	8	4	Increased cell death in myocytes <i>in vitro</i>	
Anti-Alpha-MHC (cardiac-specific)	17–37* <sup>a</sup>	20–46* <sup>a</sup>	4–16	0–2.5	Negative predictors, pro-apoptotic	109,51 <sup>a</sup> ,60 <sup>a</sup> , 118 <sup>a</sup> ,140 <sup>a</sup>
Anti-Beta-MHC (muscle-cross reactive)						68,95,96
Anti-MLC 1v	NT	17 <sup>^</sup> –35	25	0–15		51,67 <sup>^</sup>
Anti-tropomyosin	NT	55 <sup>^</sup>	21	NT		67
Anti-non-myofibrillar	NT	46* <sup>a</sup>	17	0		51 <sup>a</sup>
Anti-MHC	NT	67 <sup>^</sup>	42	NT		67
Anti-actin	NT	71 <sup>^</sup>	21	NT		67
Anti-Troponin I, T	NT	1.7 <sup>^</sup> –20 <sup>^</sup>	0 <sup>^</sup> –18	0–4	Negative predictors	66,68,80
Anti-laminin	73	78	25–35	6		97
Anti-HSP60,70	NT	10–85 <sup>^</sup>	1–42	3		67,79
Anti-s.Na/K-ATPase	26*		NT	2	Ventricular tachycardia predictors	49
Anti- ANT	91* <sup>a</sup>	57* <sup>a</sup>	0	0	Negative inotropic	81–83 <sup>a</sup>
Anti-M7	13*	31*	10	0		65
Anti-BCKD-E2	100* <sup>^</sup>	60* <sup>^</sup>	4	0		46

Legend to Table 2: \*P < 0.05 vs. normals; <sup>^</sup>P < 0.05 vs. OCD.

AFA, anti-fibrillary Ab; AHA, organ-specific and partially organ-specific anti-heart aabs; AIDA, anti-intercalated disks-aabs; ANT, adenine nucleotide translocator; AMLA, anti-myolemmal aabs; AR, adrenergic receptor; ASA, anti-sarcolemmal aabs; IFA, anti-interfibrillary aabs; BCKD, branched chain alpha-ketoacid dehydrogenase dihydrolipoyl transacylase; HSP, heat shock protein; NT, not tested; OCD, other cardiac disease; MHC, myosin heavy chain; MLC1v, myosin light chain 1 ventricular; Myoc, myocarditis.

<sup>a</sup>Cardiac and disease-specific for myocarditis/DCM.

<sup>b</sup>Increase L-type Ca<sup>2+</sup> current; short-term positive inotropic effects; increase in cytoplasmic cAMP, and cAMP/ FRET-activity.

<sup>c</sup>77% (in Chagas-DCM).

<sup>d</sup>In atrial fibrillation patients.

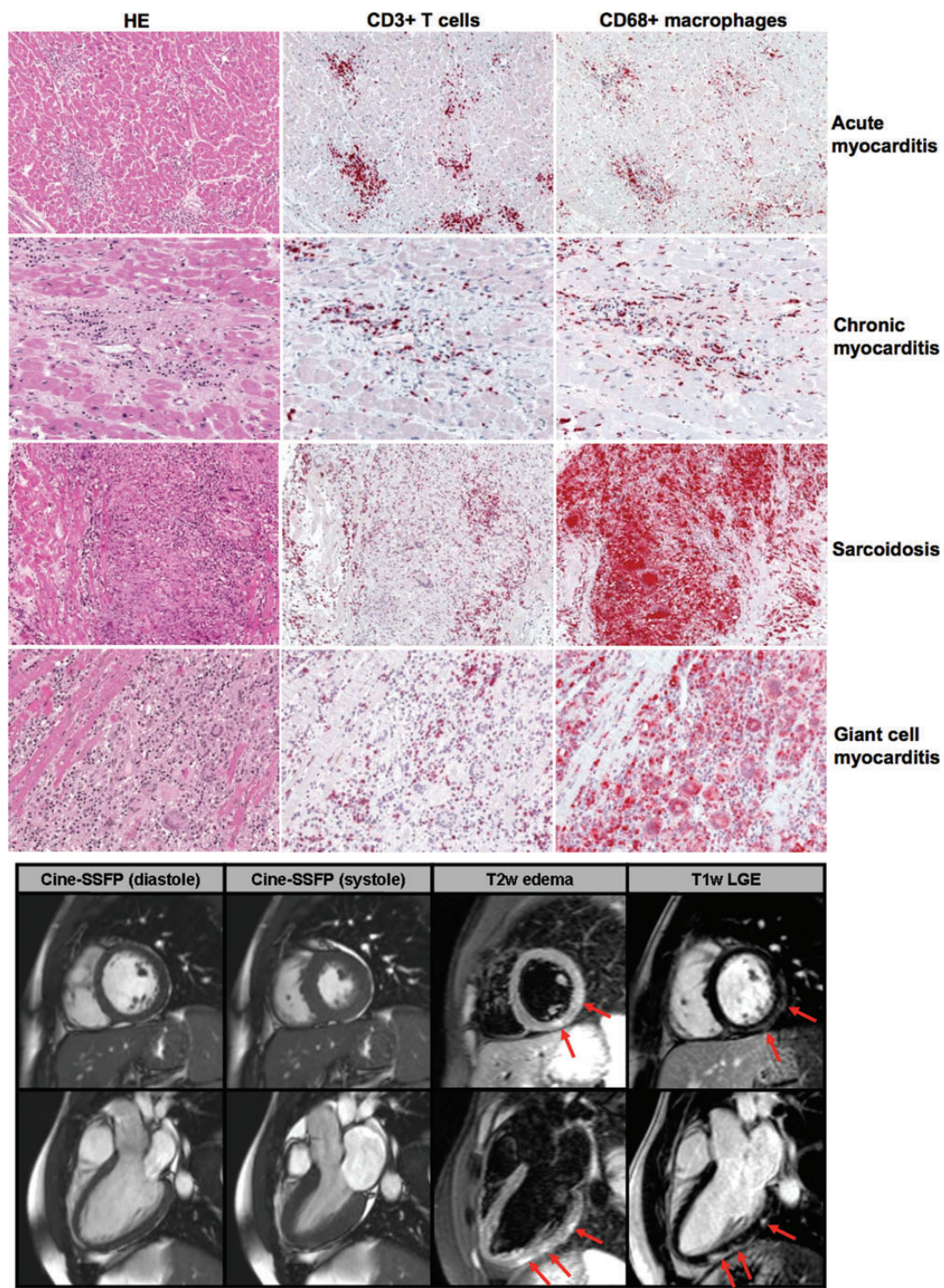
<sup>e</sup>In selected ELISA-positive heart failure patients.

## Diagnosis of myocarditis

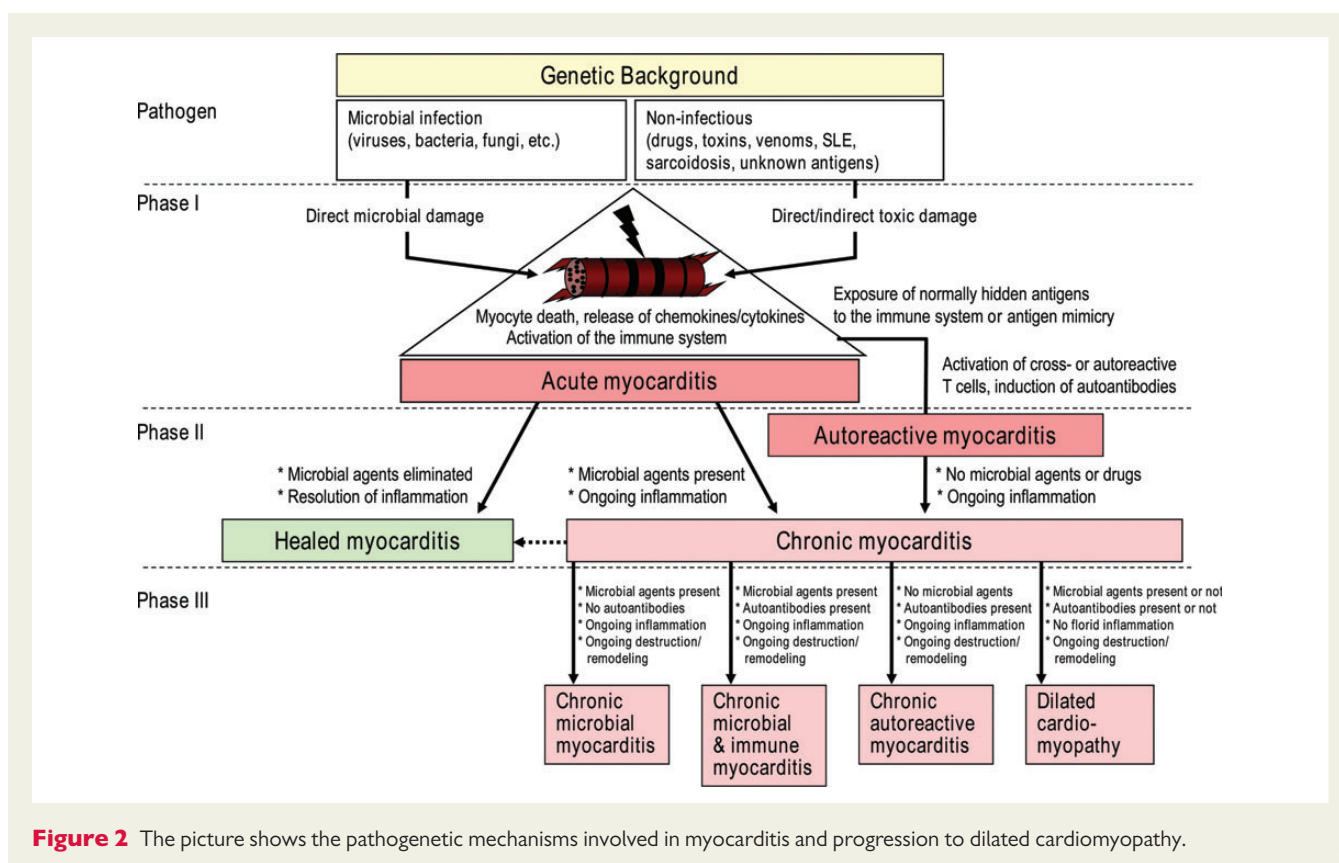
Non-invasive imaging techniques such as cardiac magnetic resonance (CMR) imaging can be useful in making the diagnosis of myocarditis and for monitoring disease progression, but we strongly endorse the

concept that EMB should be the gold standard for the diagnosis of definite myocarditis.<sup>1–3</sup> However, this implies that all patients with suspected myocarditis should undergo an EMB which is not routine practice; moreover, current guidelines recommend EMB only in a limited number of clinical scenarios that do not include some common





**Figure 1** Upper panel: histopathology and immunopathology of acute lymphocytic myocarditis (first row,  $\times 100$ ), chronic lymphocytic myocarditis (second row,  $\times 200$ ), sarcoidosis (third row,  $\times 100$ ), and giant cell myocarditis (fourth row,  $\times 200$ ). Left column = haematoxylin-eosin (HE); middle column = staining with anti-CD3 antibody (pan T lymphocyte marker); right column = staining with anti-CD68 antibody (macrophage marker). Lower panel: short-axis (upper line) and long-axis (lower line) CMR images of a young patient with acute myocarditis. In the first two columns, cine-SSFP images are shown in diastole and systole and suggest absence of any wall motion abnormality. In the next column, T2-weighted edema images demonstrate the presence of patchy focal edema in the subepicardium of the inferolateral wall (red arrows). In the last column, T1-weighted LGE images demonstrate presence of subepicardially distributed LGE (red arrows) which is typical for acute myocarditis.



**Figure 2** The picture shows the pathogenetic mechanisms involved in myocarditis and progression to dilated cardiomyopathy.

presentations of myocarditis, in particular, pseudo-infarction.<sup>120</sup> In order to improve recognition of myocarditis in clinical practice and to aid selection of patients that require further diagnostic evaluation and treatment, we propose new criteria for clinically suspected myocarditis for which biopsy analysis is recommended (Table 4). These criteria are based upon consensus of experts and require validation in future multicentre registries and randomized trials in patients who have undergone EMB. Medical centres that cannot safely perform EMB or do not have access to state-of-the-art CMR should refer patients with clinically suspected myocarditis to a tertiary referral unit experienced in EMB and CMR, particularly when patients present with haemodynamic instability or life-threatening arrhythmia.

## Firstline tests in patients with a clinical presentation consistent with myocarditis

### Electrocardiogram (ECG)

Electrocardiogram (ECG) is usually abnormal in myocarditis though ECG signs are neither specific nor sensitive (Table 4).<sup>9,121,122</sup> Some ECG changes are more suggestive of myocarditis than others. For example, ST-T segment elevation in myocarditis is typically concave (rather than convex in myocardial ischaemia) and diffuse without reciprocal changes. A-V block in the presence of mild left ventricular dilatation can be due to various causes (including laminopathy), but it may also be suggestive of Lyme disease, cardiac sarcoidosis, or giant cell myocarditis. In recent studies, QRS prolongation was an independent negative predictor for survival (which could be also due solely to asynchrony in left bundle branch block), while Q-waves and repolarization

abnormalities were unrelated to outcome or immunohistological features of inflammation on EMB.<sup>122</sup>

#### Recommendation

1. Standard 12-lead electrocardiogram should be performed in all patients with clinically suspected myocarditis.

### Echocardiography

Echocardiography helps to rule out non-inflammatory cardiac disease such as valve disease and to monitor changes in cardiac chamber size, wall thickness, ventricular function, and pericardial effusions. Global ventricular dysfunction, regional wall motion abnormalities, and diastolic dysfunction with preserved ejection fraction may occur in myocarditis.<sup>123,124</sup> Histologically proven myocarditis may resemble dilated, hypertrophic, and restrictive cardiomyopathy and can mimic ischaemic heart disease.<sup>124,125</sup> Fulminant myocarditis often presents with a non-dilated, thickened, and hypocontractile left ventricle as the intense inflammatory response results in interstitial oedema and loss of ventricular contractility.<sup>123,124</sup> The role of newer imaging techniques such as tissue Doppler or strain-rate imaging in the diagnosis of myocarditis remains to be determined.

#### Recommendations

2. All patients with clinically suspected myocarditis should undergo a standard trans-thoracic echocardiogram at presentation.
3. Trans-thoracic echocardiogram should be repeated during hospitalization if there is any worsening of haemodynamics.



**Table 3** Clinical presentations of patients with biopsy-proven inflammatory heart muscle disease

- (1) Acute coronary syndrome-like
  - (a) Acute chest pain
    - Frequently starting within 1–4 weeks of a respiratory or gastrointestinal infection
    - Frequently associated with severe and recurrent symptoms
    - In the absence of angiographic evidence of CAD
  - (b) ST/T wave changes
    - ST-segment elevation or depression
    - T-wave inversions
  - (c) With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR
  - (d) With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months
- (2) New onset or worsening heart failure in the absence of CAD and known causes of heart failure
  - (a) New onset or progressive heart failure over 2 weeks to 3 months
    - Dyspnoea
    - Peripheral oedema
    - Chest discomfort
    - Fatigue
  - (b) Impaired systolic LV and/or RV function, with or without an increase in wall thickness, with or without dilated LV and/or RV on echocardiography or CMR
  - (c) Symptoms possibly started after a respiratory or gastrointestinal infection, or in the peri-partum period
  - (d) Non-specific ECG signs, bundle branch block, AV-block, and/or ventricular arrhythmias
- (3) Chronic heart failure in the absence of CAD and known causes of heart failure (see point 2 above)
  - (a) Heart failure symptoms (with recurrent exacerbations) of > 3 months duration
  - (b) Fatigue, palpitation, dyspnoea, atypical chest pain, arrhythmia in an ambulant patient
  - (c) Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of DCM or non-ischaemic cardiomyopathy
  - (d) Non-specific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block
- (4) 'life-threatening condition', in the absence of CAD and known causes of heart failure comprising
  - (a) Life-threatening arrhythmias and aborted sudden death
  - (b) Cardiogenic shock
  - (c) Severely impaired LV function

**Nuclear imaging**

Data on radionuclide evaluation, including antimyosin antibody imaging, are scarce but suggest that its sensitivity for detecting myocardial inflammation is variable and its specificity low.<sup>125–128</sup> Due to their limited availability and risk from radiation exposure, nuclear techniques are not routinely recommended for the diagnosis of myocarditis, with the possible exception of sarcoidosis.

Thallium 201 and technetium 99m scintigraphy have been used to detect cardiac sarcoidosis but lack specificity. Gallium-67 scintigraphy and more recently positron emission tomography using 18 fluorodeoxyglucose are probably more sensitive and may be useful in the acute phase of sarcoidosis and to monitor disease progression.<sup>129–132</sup> The detection of extracardiac disease can suggest a diagnosis of cardiac sarcoidosis.

Recommendations

- 4. Nuclear imaging is not routinely recommended in the diagnosis of myocarditis, with the possible exception of suspected cardiac sarcoidosis.

**Cardiovascular magnetic resonance (CMR) imaging**

Cardiovascular magnetic resonance imaging provides non-invasive tissue characterization of the myocardium and can support the diagnosis of myocarditis (Figure 1).<sup>133–139</sup> The timing of CMR in suspected myocarditis will depend upon local availability and expertise, but it is reasonable to first perform CMR in clinically stable patients, prior to EMB. It should not be performed in life-threatening presentations where EMB is urgently indicated.<sup>120,139</sup> Cardiovascular magnetic resonance imaging techniques have been evaluated in animal models of myocarditis as well as in patients.<sup>19,20,125,133–139</sup> Based on pre-clinical and clinical studies, an 'International Consensus Group on CMR Diagnosis of Myocarditis' published detailed recommendations on the indication, implementation, and analysis of appropriate CMR techniques for non-invasive diagnosis of myocarditis (Lake Louise criteria).<sup>20</sup> The combined use of three different CMR techniques is suggested (Table 5).<sup>134,136–139</sup> One study has demonstrated good correlation between CMR and EMB in troponin-positive patients without coronary artery disease<sup>133</sup>; however, correlation is worse in patients with a longer history of symptoms and histologically confirmed

**Table 4** Diagnostic criteria for clinically suspected myocarditis

Clinical presentations <sup>a</sup>	
Acute chest pain, pericarditic, or pseudo-ischaemic	
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs	
Subacute/chronic (> 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs	
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death	
Unexplained cardiogenic shock	
Diagnostic criteria	
I. ECG/Holter/stress test features	Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
II. Mycardiocytolysis markers	Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)	New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR	Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if  $\geq 1$  clinical presentation and  $\geq 1$  diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis  $\geq 50\%$ ); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

<sup>a</sup>If the patient is asymptomatic  $\geq 2$  diagnostic criteria should be met.

chronic myocarditis and in addition CMR cannot exclude viral forms of myocarditis.<sup>137</sup>

#### Recommendations

- Cardiovascular magnetic resonance findings consistent with myocarditis should be based on Lake-Louise criteria (Table 5).
- Cardiovascular magnetic resonance may be considered in clinically stable patients prior to EMB. Cardiovascular magnetic resonance does not replace EMB in the diagnosis of myocarditis and should not delay EMB in life-threatening presentations.

### Biomarkers

#### Inflammatory markers

Erythrocyte sedimentation rate and reactive C protein levels are often raised in myocarditis, but they do not confirm the diagnosis and are often increased in acute pericarditis.<sup>52</sup>

#### Troponin and BNP levels

While cardiac troponins are more sensitive of myocyte injury in patients with clinically suspected myocarditis than creatine kinase levels,<sup>140,141</sup> they are non-specific and when normal do not exclude myocarditis.<sup>142</sup> This also applies to cardiac hormones such as brain natriuretic peptides,<sup>143</sup> circulating cytokines,<sup>144</sup> markers related to extracellular matrix degradation,<sup>145</sup> and new biomarkers such as pentraxin 3, galectin 3, and growth differentiation factor 15.<sup>146</sup>

#### Viral antibodies

Positive viral serology does not imply myocardial infection but rather indicates the interaction of the peripheral immune system with an infectious agent. Polyclonal stimulation of antibodies (IgM and IgG) may furthermore lead to incorrect diagnosis. Thus, viral serology is of limited utility in the diagnosis of viral myocarditis<sup>147</sup> because the prevalence of circulatory IgG antibodies to cardiotropic viruses in the general population is high in the absence of viral heart disease.<sup>2,16,23,25,31,105</sup> In addition, infection with non-cardiotropic enteroviruses may cause an antibody response which is indistinguishable from the response to cardiotropic viruses<sup>2,16,23,25,31,105</sup> and, in a recent study, there was no correlation between virus serology and EMB findings.<sup>147</sup> Circumstances in which serological testing may be helpful include suspected hepatitis C, rickettsial phase 1 and phase 2, Lyme disease in endemic areas, and human immunodeficiency in high-risk patients.

#### (b) Serum cardiac autoantibodies (aabs)

Aabs to various cardiac and muscle-specific autoantigens are found in myocarditis and in DCM patients (Table 2).<sup>9,35,36,46–98,109,118</sup> Lack of viral genome on EMB with detectable serum aabs suggests immune-mediated DCM or myocarditis.<sup>9,15,16,100</sup> Antibodies of IgG class, which are shown to be cardiac and disease-specific for myocarditis/ DCM, can be used as auto-immune biomarkers for identifying at risk relatives and those patients in whom, in the absence of active infection of the myocardium, immunosuppression and/or immunomodulation may be beneficial.<sup>9,15,16,35,36,100,118</sup> Detection of cardiodepressant antibodies in DCM also predicts haemodynamic benefits from



**Table 5** Diagnostic cardiac magnetic resonance criteria for myocarditis

In the setting of clinically suspected myocarditis (Tables 3–4), CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

- (1) Regional or global myocardial signal intensity increase in T2-weighted oedema images<sup>a</sup>
- (2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images<sup>b</sup>
- (3) There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)<sup>c</sup>

A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present

A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if

- None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation
- One of the criteria is present

The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis

Table reprinted with permission from (20).

<sup>a</sup>Global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of  $\geq 2.0$ . If the edema is more subendocardial or transmural in combination with a colocalized ischaemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.

<sup>b</sup>A global SI enhancement ratio of myocardium over skeletal muscle of  $\geq 4.0$  or an absolute myocardial enhancement of  $\geq 45\%$  is consistent with myocarditis.

<sup>c</sup>Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

immunoabsorption.<sup>85</sup> Some aabs have been described to be negative predictors in myocarditis or DCM<sup>90,95</sup> (Table 2). At present, no commercially available cardiac autoantibody tests have been validated against the results obtained in research laboratories; collaborative work among European research antibody laboratories is in progress to overcome this difficulty.<sup>37</sup>

Recommendations

7. Troponins, erythrocyte sedimentation rate, reactive C protein levels should be assessed in all patients.
8. Routine viral serology testing is not recommended.
9. Serum samples should be assessed, if possible, for cardiac aabs, if one (or more) of the published tests is available (Table 2), according to specific centre expertise. Disease-specific aabs should preferably be tested.

**Proposed criteria for clinically suspected myocarditis**

In this position statement, we propose new criteria for the diagnosis of clinically suspected myocarditis. These are based on a clinical presentation consistent with the diagnosis (Table 3) and the presence of one or more abnormalities on non-invasive testing (Table 4).

Myocarditis should be suspected in the presence of:

- 1 or more of the clinical presentations in Table 4, with or without ancillary features (see below), and
  - 1 or more of the diagnostic criteria from different categories (I to IV) in Table 4
- or
- when the patient is asymptomatic, 2 or more diagnostic criteria from different categories (I to IV).

Ancillary features which support the clinical suspicion of myocarditis include:

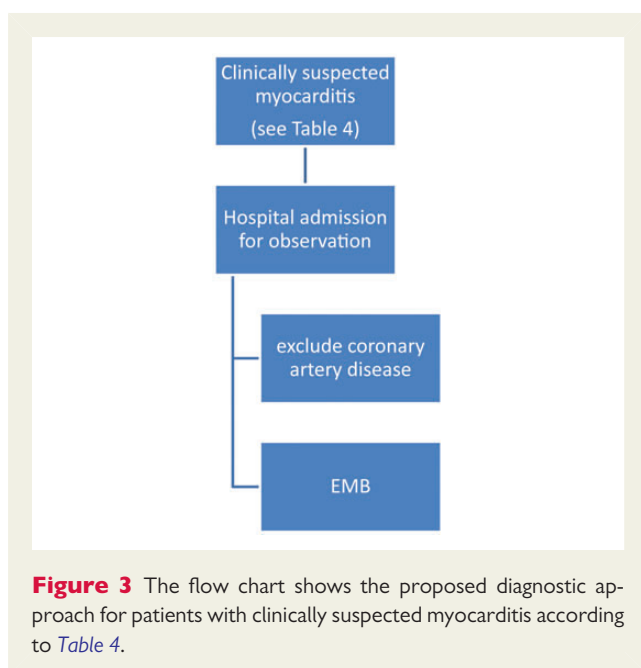
- Fever  $\geq 38.0^{\circ}\text{C}$  at presentation or within the preceding 30 days with or without evidence of a respiratory (chills, headache, muscle aches, general malaise) or gastrointestinal (decreased appetite, nausea, vomiting, diarrhoea) infection;
- peri-partum period<sup>121</sup>;
- previous clinically suspected or definite myocarditis (according to the criteria set in Table 4);
- personal and/or family history of allergic asthma, other types of allergy, extra-cardiac autoimmune disease, toxic agents;
- family history of DCM, myocarditis (according to the present criteria).

Recommendation

10. All patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB.

**Second level investigations in clinically suspected myocarditis**

In patients fulfilling the diagnostic criteria for clinically suspected myocarditis, we recommend selective coronary angiography and EMB (Figure 3). This recommendation also applies to patients with an acute coronary syndrome-like presentation (with or without ST segment elevation), increased cardiac troponins, preserved ventricular systolic function with or without features suggestive of myocarditis on CMR (Figure 1).<sup>20</sup> At present, there are limited data on the prognostic implications of CMR findings in this context, and this common scenario was not included in a recently published AHA/ACC/HFSA scientific statement on EMB.<sup>120</sup> Therefore, in the absence of robust prospective data (in suspected myocarditis with pseudo-infarct presentation and



normal coronary arteries), the definitive diagnosis of myocarditis should still be based on EMB (Figure 3).

## Endomyocardial biopsy

Endomyocardial biopsy confirms the diagnosis of myocarditis and identifies the underlying aetiology and the type of inflammation (e.g. giant cell, eosinophilic myocarditis, sarcoidosis) which imply different treatments and prognosis (Figure 1).<sup>1–3,11,14–16</sup> Importantly, EMB is also the basis for safe (infection negative) immunosuppression and antiviral treatment. If EMB is performed by experienced teams, its complication rate is low (0–0.8).<sup>9,18,139,148</sup>

The recent scientific statement on EMB gave highest levels of recommendations in the life-threatening clinical presentations.<sup>120</sup> However, the diagnostic, prognostic, and therapeutic value of EMB was based on the Dallas histopathologic criteria and did not include immunohistochemistry and viral genome analysis (Figure 1). These are established tools which should be used to achieve an aetiological diagnosis.<sup>9,14–16,18,19,22,26,30–32,100,101,103,133,137,138</sup>

To optimize diagnostic accuracy and reduce sampling error in focal myocarditis, EMB should be performed early in the course of the disease and multiple specimens should be taken.<sup>2</sup> At least three samples, each 1–2 mm in size, should be taken (from the right or from the left ventricle) and immediately fixed in 10% buffered formalin at room temperature for light microscopy; additional samples should be snap frozen in liquid nitrogen and stored at  $-80^{\circ}\text{C}$  or stored in RNA later tubes at room temperature for viral PCR.<sup>2,149</sup> With respect to left or right heart biopsy, some patients may clinically present with exclusive left or right heart failure and myocarditis. In such cases, decision for left or right heart biopsy should be made according to the additional clinical information. To increase the diagnostic sensitivity of immunohistochemistry, use of a large panel of monoclonal and polyclonal antibodies (including anti-CD3, T lymphocytes; anti-CD68, macrophages; and anti HLA-DR) is mandatory for the identification and characterization of the inflammatory infiltrate

and for the detection of HLA-DR upregulation on EMB tissue sections as marker of infectious-negative autoimmune myocarditis where immunosuppression may be considered.<sup>2,14,15</sup> Other immunofluorescence stains used to define humoral rejection in heart transplant EMB, such as C3d and C4d, have been recently reported as promising markers of immune activation in patients with inflammatory cardiomyopathy; a limitation of these stains is that they require frozen material.<sup>40</sup>

The diagnostic contribution of EMB is enhanced by molecular analysis with DNA–RNA extraction and RT-PCR amplification of viral genome.<sup>16</sup> In order to exclude systemic infection, peripheral blood should be investigated in parallel with EMB<sup>2,9</sup>; quantification of virus load and determination of virus replication may add diagnostic value.<sup>22</sup>

Suggested primer sets and PCR protocols are detailed in the supplementary material online, appendix. The main technical requirements are as follows:

- RT-PCR detection of viral DNA or RNA in the heart should always be controlled by amplifying adequate positive samples containing different viral copy numbers as well as negative controls.<sup>2</sup> Sequencing of the amplified viral gene product is mandatory in order to identify virus subtypes and recognize contaminations.
- Blood samples should be tested by RT-PCR to detect acute systemic virus infection, and to exclude persistently/latently infected blood cells which might contaminate heart tissue samples but do not indicate virus infection of the myocardium.<sup>2</sup>
- The detection of replicative forms of viral nucleic acids in the heart supports a pathogenic role of virus in myocarditis; however, detection of viral mRNA by RT-PCR may be difficult to establish in EMB due to low amounts of viral mRNA especially in longstanding chronic myocarditis.

### Recommendations

11. Tissue obtained from EMB should be analysed using histology, immunohistochemistry, and viral PCR (on heart tissue and a blood sample).
12. At least three myocardial samples, each 1–2 mm in size, should be taken (from the right or from the left ventricle) and immediately fixed in 10% buffered formalin at room temperature for light microscopy; additional samples should be taken, snap frozen in liquid nitrogen, and stored at  $-80^{\circ}\text{C}$ , or stored in RNA later tubes at room temperature, for viral PCR.<sup>2,149</sup>
13. Endomyocardial biopsy may be repeated if necessary to monitor response to aetiology-directed therapy, or if a sampling error is suspected in a patient with unexplained progression of heart failure.

## Clinical management

Outcome and prognosis of myocarditis depends on aetiology, clinical presentation, and disease stage.<sup>3,9–11</sup> Acute myocarditis resolves in about 50% of cases in the first 2–4 weeks, but about 25% will develop persistent cardiac dysfunction and 12–25% may acutely deteriorate and either die or progress to end-stage DCM with a need for heart transplantation.<sup>1–3,6–9,16,150</sup> Biventricular dysfunction at presentation has been reported as the main predictor of death or

transplantation.<sup>1–3,6–9,16,150</sup> Fulminant myocarditis is said to differ from (sub)acute lymphocytic myocarditis in its mode of onset, degree of haemodynamic compromise, and better outcome, but data are relatively scarce in adult patients.<sup>150</sup> Fulminant myocarditis of unknown aetiology is more frequent in children and prevalent in neonates with a dismal prognosis.<sup>10</sup> Most studies suggest that survival rates in giant-cell myocarditis are markedly worse.<sup>3,9,11,34,99</sup>

Molecular detection techniques for viral genome in EMB specimens have provided conflicting prognostic information.<sup>9,18,32,151–153</sup> Viral persistence in the myocardium has been associated with ventricular dysfunction and viral genome clearance with improvement of ventricular function and a better 10-year prognosis.<sup>32,152</sup> In contrast, in a recent report, immunohistological evidence of inflammation but not the presence of viral genome alone was an independent predictor of survival.<sup>18</sup> This discrepancy may relate to the variability in the viral epidemiology of different populations and to low numbers of events.

The frequency of specific viruses among patients who recover spontaneously is largely unknown. This may also confer some bias to the published studies on prognosis.<sup>9,18,32,151–153</sup> The molecular mechanisms responsible for the reactivation of latent viral infection, the influence of immune activation triggering viral replication in chronic myocarditis, and immune-independent viral pathogenesis in non-inflamed hearts are remaining gaps in the understanding of viral pathogenicity.<sup>22</sup>

## (a) Conventional medical treatment

As large multicentre randomized controlled trials examining distinct pathogenic subsets are not available,<sup>10</sup> recommendations are based on the consensus of the expert Task Force. The core principles of treatment in myocarditis are optimal care of arrhythmia and of heart failure and, where supported by evidence, aetiology-targeted therapy.

### 1. Haemodynamically unstable patients

Patients with haemodynamically unstable heart failure should be managed promptly according to current ESC guidelines for heart failure<sup>154</sup> in intensive care units with respiratory and mechanical cardio-pulmonary support facilities. In acute/fulminant cases with cardiogenic shock and severe ventricular dysfunction, ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be needed to provide a bridge to transplant or to recovery.<sup>10,155–157</sup> Because of its simplicity and effectiveness, ECMO therapy can rescue this group of patients.<sup>156,157</sup>

#### Recommendations

14. Patients with a life-threatening presentation should be sent to specialized units with capability for haemodynamic monitoring, cardiac catheterization, and expertise in EMB.
15. In patients with haemodynamic instability, a mechanical cardio-pulmonary assist device may be needed as a bridge to recovery or to heart transplantation.
16. Cardiac transplantation should be deferred in the acute phase, because recovery may occur, but can be considered for haemodynamically unstable myocarditis patients, including those with giant cell myocarditis, if optimal pharmacological support and mechanical assistance cannot stabilize the patient.

### 2. Haemodynamically stable patients

When myocarditis is suspected in asymptomatic or mildly symptomatic patients according to the criteria shown in *Table 4*, admission to hospital and clinical monitoring are recommended until a definite diagnosis is established, since the situation can evolve rapidly and a cardiopulmonary emergency (e.g. severe heart block or life-threatening arrhythmia) is possible and unpredictable, even if systolic function is initially preserved.<sup>10</sup> Exercise testing is contraindicated in the acute stage as it can precipitate arrhythmia.

Patients with haemodynamically stable heart failure should be treated with diuretics, angiotensin-converting enzyme inhibitor, or angiotensin receptor blockade and beta-adrenergic blockade. In patients who have persistent heart failure symptoms despite optimal management, additional treatment with aldosterone antagonists should be considered.<sup>154</sup> The procedure for weaning of heart failure therapy following recovery of ventricular function is not defined.

Non-steroidal anti-inflammatory drugs, in particular acetylsalicylic acid, are a cornerstone of treatment for acute pericarditis, but have been associated with increased mortality in experimental models of myocarditis.<sup>106–108</sup> Clinical data for their administration in myocarditis are inconclusive, and controlled trials are needed.

#### Recommendations

17. Management of ventricular dysfunction should be in line with current ESC guidelines on heart failure.

### 3. Arrhythmia

There are no specific recommendations for the management of arrhythmia in myocarditis, and so management should be in line with current ESC guidelines.<sup>157–162</sup> Sinus bradycardia, prolonged QRS duration, increased left ventricular hypokinesia on echocardiography, persistent or fluctuating cardiac troponin levels may precede a life-threatening arrhythmia.<sup>10</sup> Temporary pacing may be needed for complete atrio-ventricular block.<sup>10</sup> Indication for cardioverter defibrillator implantation (ICD) is controversial, because myocarditis may heal completely. Bridging by a lifevest in patients with myocarditis and severe ventricular arrhythmia (ventricular tachycardia or fibrillation) could solve the transient problem.<sup>163</sup>

#### Recommendations

18. ICD implantation should be deferred until resolution of the acute episode.
19. Arrhythmia management outside the acute phase should be in line with current ESC guidelines on arrhythmia and device implantation.

### 4. Avoidance of exercise

Physical activity should be restricted during the acute phase of myocarditis until the disease has completely resolved.<sup>164,165</sup> Athletes should be temporarily excluded from competitive and amateur-leisure time sport activity regardless of age, gender, severity of symptoms, or therapeutic regimen.<sup>164,165</sup> After resolution of the clinical presentation (at least 6 months after the onset of the disease), clinical

reassessment is indicated before the athlete resumes competitive sport.<sup>164,165</sup> Pre-participation screening should be performed every 6 months during the follow-up.<sup>164,165</sup> Although the duration of restricted physical activity in non-athletes is undefined, based upon expert opinion of this Task Force, it seems reasonable to give similar recommendations.

#### Recommendation

20. Physical activity should be restricted during the acute phase of myocarditis and for at least 6 months in athletes and non-athletes. This recommendation is based upon expert opinion of this Task Force.

## (b) Immunomodulatory therapy

### Anti-viral therapies

There is still no approved antiviral-therapy for the treatment of enteroviral infections. Vaccines may be an option in the future.<sup>166</sup> Treatment with acyclovir, gancyclovir, and valacyclovir may be considered in patients with herpes virus infection,<sup>167</sup> although their efficacy is unproven in myocarditis. Preliminary data on interferon-beta treatment suggest that it eliminates enteroviral and adenoviral genomes in patients with left ventricular dysfunction,<sup>168</sup> is associated with improvement in NYHA functional class,<sup>169</sup> and, specifically in enteroviral infection, with a better 10-year prognosis.<sup>152</sup> In general, we recommend involvement of infectious disease specialists when deciding on the use of specific antiviral therapies.

### High dose intravenous immunoglobulin

High dose intravenous immunoglobulin (IVIG) modulates the immune and inflammatory response by a variety of mechanisms and is used in a number of systemic autoimmune diseases.<sup>170</sup> Its use has been associated with improved left ventricular ejection fraction in chronic symptomatic heart failure of various causes,<sup>171</sup> but IVIG was ineffective in the IMAC controlled trial of recent-onset DCM in which only 15% of patients had biopsy-proven myocarditis of non-specified cause.<sup>172</sup> Nevertheless, IVIG has no major side-effects and may be used in myocarditis refractory to conventional heart failure therapy, both viral and autoimmune forms, particularly if autoantibody-mediated.<sup>3</sup> In the absence of multi-centre randomized studies in biopsy-proven myocarditis/DCM of viral or autoimmune origin, we do not give recommendations for the use of IVIG.

### Immunoabsorption (IA)

Various aabs have been detected in myocarditis and DCM patients and for some a pathogenic role has been proposed (Table 2). Thus, therapeutic strategies used in other auto-immune disorders,<sup>173–175</sup> such as neutralization or immunoabsorption (IA) of disease-causing aabs, might offer treatment options for autoimmune myocarditis/DCM. Small randomized studies with DCM patients have shown that IA induces improvement of LV function and decreases myocardial inflammation<sup>76,102</sup>; a larger randomized controlled clinical trial is currently underway in Europe. Until these results are available, we do not give recommendations for the use of immunoabsorption.

## (c) Immunosuppressive therapy

Most data on safety and efficacy of immunosuppressive regimes in myocarditis have been obtained using steroids alone, azathioprine and steroids, or cyclosporine A, azathioprine and steroids. Information on other drugs is not available. Data from the few randomized clinical trials of immunosuppression in myocarditis and DCM are shown in Table 6. Response to therapy is reported mainly in chronic virus-negative forms, in giant cell myocarditis, and in active myocarditis defined as autoimmune (e.g. virus-negative and autoantibody positive). Conversely, immunosuppression had a neutral effect in the Myocarditis Treatment Trial, where patients had myocarditis of unknown aetiology.<sup>6</sup>

It is necessary to identify possible drugs causing hypersensitivity reactions, particularly in patients with hypereosinophilia<sup>10</sup>; the inducing drug (Table 1) should not be reintroduced after recovery.<sup>10</sup>

Recently, a single-centre controlled trial suggested a beneficial effect of combined steroid and azathioprine therapy in virus-negative myocarditis.<sup>101</sup> These data need to be confirmed in multicentre studies.

#### Recommendations

21. Immunosuppression should be started only after ruling out active infection on EMB by PCR.
22. Based on experience with non-cardiac autoimmune disease, the task group recommends consideration of immunosuppression in proven autoimmune (e.g. infection-negative) forms of myocarditis, with no contraindications to immunosuppression, including giant cell myocarditis, cardiac sarcoidosis, and myocarditis associated with known extra-cardiac autoimmune disease.<sup>10,99</sup>
23. Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia and in some forms of infection-negative eosinophilic or toxic myocarditis with heart failure and/or arrhythmia.
24. Immunosuppression may be considered, on an individual basis, in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression.
25. Follow-up EMB may be required to guide the intensity and the length of immunosuppression.

## (d) Follow-up

Myocarditis patients can have partial or full clinical recovery; some may relapse many years after the first episode. Relapses should be managed similarly to the index episode. In patients who do not resolve, disease may continue subclinically and lead to DCM.

The myocarditis patient with pseudo-infarct presentation, normal coronary arteries, and preserved ventricular function should be discharged when cardiac enzymes have come into the normal range, and offered long-term non-invasive cardiological follow-up. In the event of prolonged (weeks or even months) documented increase of cardiac enzymes, and/or progressive reduction in left and/or right ventricular function, the patient should be readmitted to hospital to perform EMB.



**Table 6** Controlled immunosuppression trials in myocarditis and dilated cardiomyopathy

Trial	Year	Type	Pts (n)	Diagnosis	Primary endpoint	Results	Author <sup>ref</sup>
Prednisone trial for DCM	1989	Randomized controlled trial (RCT): prednisone (PDN)	102	'Reactive' DCM (n = 60) 'Nonreactive DCM' (n = 42)	Either higher LV ejection fraction (LVEF) at 3 months or lower LV end-diastolic dimension and better exercise tolerance	Favourable	Parrillo <sup>176</sup>
MTT	1995	RCT: PDN and cyclosporine or azathioprine	111	Acute biopsy-proven myocarditis (unknown aetiology)	LVEF at 6 months	Neutral	Mason <sup>6</sup>
Giant cell myocarditis treatment trial	2008	Prospective: PDN and cyclosporine	11	Giant cell myocarditis (autoimmune)	Survival at 1 year	Favourable	Cooper <sup>99</sup>
	2003	Prospective: PDN and azathioprine	41	Active myocarditis and chronic heart failure (aetiology known in retrospect)	LVEF at 1 year	Favourable in virus-negative aabs-positive autoimmune forms	Frustaci <sup>100</sup>
	2001	RCT: PDN and azathioprine	84	Inflammatory DCM (unknown aetiology, increased HLA expression on EMB)	LVEF at 3 months, sustained at 2 years	Favourable	Wojnicz <sup>103</sup>
TIMIC	2009	RCT: PDN and azathioprine	85	Inflammatory virus-negative DCM	LVEF at 6 months	Favourable	Frustaci <sup>101</sup>

Persistently elevated troponin T values could be due to heterophile antibodies interfering with the assay. Performing a troponin I could clarify whether persistent enzyme elevations are due to an analytic error or cardiac pathology. Similarly, chronic skeletal muscle disease could be associated with persistently elevated low level cardiac troponins.

#### Recommendations

26. All patients with myocarditis should be followed, with clinical assessment, ECG, and echocardiography.
27. Long-term follow-up for patients that have experienced myocarditis is recommended.

## Summary

This position statement reviews current knowledge, and proposes new diagnostic criteria for clinically suspected myocarditis and its distinct biopsy-proven pathogenetic forms. The aims are to bridge the gap between clinical and tissue-based diagnosis, to improve management and provide a common reference point for future registries and multicentre randomized controlled trials of aetiology-driven treatment in inflammatory heart muscle disease.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

**Conflict of interest:** none declared.

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