



# Myocarditis and cardiomyopathy

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## Purpose of review

The aim of this study is to summarize the literature describing the pathogenesis, diagnosis and management of cardiomyopathy related to myocarditis.

## Recent findings

Myocarditis has a variety of causes and a heterogeneous clinical presentation with potentially life-threatening complications. About one-third of patients will develop a dilated cardiomyopathy and the pathogenesis is a multiphase, multicompartiment process that involves immune activation, including innate immune system triggered proinflammatory cytokines and autoantibodies. In recent years, diagnosis has been aided by advancements in cardiac MRI, and in particular T1 and T2 mapping sequences. In certain clinical situations, endomyocardial biopsy (EMB) should be performed, with consideration of left ventricular sampling, for an accurate diagnosis that may aid treatment and prognostication.

## Summary

Although overall myocarditis accounts for a minority of cardiomyopathy and heart failure presentations, the clinical presentation is variable and the pathophysiology of myocardial damage is unique. Cardiac MRI has significantly improved diagnostic abilities, but endomyocardial biopsy remains the gold standard. However, current treatment strategies are still focused on routine heart failure pharmacotherapies and supportive care or cardiac transplantation/mechanical support for those with end-stage heart failure.

## Keywords

cardiac MRI, cardiomyopathy, endomyocardial biopsy, myocarditis

## INTRODUCTION

Myocarditis refers to inflammation of the myocardium and may be caused by infectious agents, systemic diseases, drugs and toxins, with viral infections remaining the most common cause in the developed countries [1]. The clinical symptoms associated with myocarditis are highly variable and may range from chest pain, palpitations and heart failure to cardiogenic shock and death [2<sup>\*</sup>]. Myocarditis may progress to a dilated cardiomyopathy (DCM) in nearly 30% of cases, and accounts for 9–16% of all nonischemic DCM among adult patients [3]. This review will focus on the recommended criteria for diagnosis, understanding the pathophysiology, treatment options and clinical outcomes.

## EPIDEMIOLOGY

Myocarditis will result in heart failure in around 12–17% of adults with a death rate of approximately 8.4 per 100 000. There are regional and temporal variations in myocarditis with a noted increased mortality from 1980 to 1995 that then declined. Men are more often affected than women with the peaks in

prevalence seen in children and young adults aged 20–30 years [1].

## CAUSE

Viral infections are the most common cause of myocarditis in Europe and the United States with a temporal variation in the most prevalent causative pathogens. From the 1950s through the 1990s, the most frequently identified virus was coxsackievirus [4]. In the late 1990s, adenovirus was the most commonly detected virus in endomyocardial biopsy (EMB)s, and more recently parvovirus B19 and Human Herpesvirus 6 are the most common viruses identified.

In areas of Asia, such as Japan, the hepatitis C virus is a common cause of myocarditis and DCM, while Central and South America literature describe

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**KEY POINTS**

- Myocarditis has variable clinical presentations, but may have deadly consequences.
- The most common viral causes for myocarditis are likely parvovirus B19 and HHV6.
- Cardiac MRI with contemporary T1 and T2 imaging is a well tolerated, accurate and noninvasive method for diagnosing myocarditis.
- When clinically indicated, endomyocardial biopsies are generally well tolerated and may help with accurate diagnosis, cause and management in patients with myocarditis.

causes such as Chagas disease, caused by the protozoa *Trypanosoma cruzi* [1]. In Africa, HIV is commonly associated with myocarditis and DCM, although coinfections with other viruses may also exist [1] (Table 1).

**PATHOPHYSIOLOGY**

The pathogenesis of myocarditis depends on the specific pathogen. However, much of our understanding into the pathogenesis and progression to an inflammatory DCM stems from animal models infected with coxsackievirus. The pathogenesis is believed to be a multiphase process that involves multiple compartments and begins with entry of the virus into myocardial cells via viral-specific receptors (coxsackiadenovirus receptor or CAR) [5,6] and subsequent direct inflammatory injury to the myocardium. This inflammation and damage to the cardiac muscle leads to the exposure of myosin that induces the body’s first line of defense against the

virus, the innate immune system via Toll-like receptors (TLRs) [7] and subsequent release of proinflammatory cytokines. The second part of the immune system response is the activation of T and B-cells. The innate immune system will in turn result in the activation of the acquired immunity with the expansion of T and B-cells resulting in inflammation along with necrosis, fibrosis and remodelling that involves different cellular compartments: the bone marrow derived compartment, the endothelial compartment that regulates the access of bone marrow derived cells to the heart, the interstitial compartment and the cardiomyocyte compartment, which interacts with the local milieu to shape the inflammatory response [8,9].

Contemporary data have provided further support for the role of B-cell mediated antiheart auto-antibodies in the development of myocarditis via passive antibody transfer in mouse models and ensuing histopathologic examination [10]. Furthermore, when compared with healthy controls, patients with inflammatory DCM were found to have higher levels of T helper (Th) 17 cells [11], an established mediator of myocarditis-associated cardiomyopathy in murine models [12]. The investigators provide evidence for a myosin-associated TLR-2 ligand mechanism that triggers Th17 cytokine formation, and potentially contributes to the development of DCM in myocarditis [11].

The progression of acute myocarditis to an inflammatory DCM, which only occurs in a subset of patients, is characterized by myocyte hypertrophy, apoptosis and fibrosis [13]. It has been shown that proinflammatory cytokines such as tumour necrosis factor (TNF)  $\alpha$ , interleukin (IL) 1 $\beta$  and IL-6 are elevated in mice with myocarditis [14], and TNF $\alpha$  and IL1 $\beta$  will depress human myocyte function *in vitro* [15]. In support of this mechanism, adult patients with DCM in fact have elevated levels of myocardial IL1 $\beta$  expression with concomitant myocardial hypertrophy and fibrosis [16]. Murine models of viral myocarditis have also shown that activation of Th2 cells and the subsequent production of IL-33 are protective from the development of DCM [17], further suggesting that patients who progress to a DCM may have genetic susceptibilities that lead to variations in the immune system response to myocardial viral infections. Other investigators have found that the persistence of virus in the myocardium is an important predictor of myocardial dysfunction [18]. Using EMB in 172 patients, they found that the continued presence of at least one of four common cardiovirulent viruses was associated with worse left ventricular ejection fraction (LVEF), and in contrast eradication of the virus was associated with a nearly 8% increase in LVEF

**Table 1.** Causes of myocarditis

Infectious	Noninfectious
Coxsackie virus	Giant cell myocarditis
Parvovirus-B19	Drug-induced hypersensitivity
Epstein–Barr virus	Sarcoidosis
Human herpes virus 6	Systemic lupus erythematosus
Adenovirus	Eosinophilic myocarditis
Streptococcus	Idiopathic
Borrelia burgdorferi	
Trypanosoma cruzi	
HIV	
Influenza	
Cytomegalovirus	
Hepatitis C	

[18]. Although the primary mechanism for the development of a DCM, persistent viral infection versus autoimmune-mediated, remains debated, it is obvious that patient outcomes depend, at least in part, on host genetic susceptibility, the type of pathogen and degree of molecular mimicry [9<sup>•</sup>].

## DIAGNOSIS

Due to the nonspecific symptoms associated with acute myocarditis, providers must maintain a high level of clinical suspicion to avoid a delay in diagnosis and treatment. Patients will often report a prodrome of fever, rash, myalgias, arthralgias, fatigue and respiratory or gastrointestinal symptoms [13]. In young adults, acute myocarditis typically presents as chest pain mimicking a myocardial infarction (MI) or pericarditis with or without elevated troponin levels [2<sup>•</sup>]. A retrospective analysis of more than 6000 patients less than 50 years old who presented with troponin elevations found that myocarditis accounted for 8% [19<sup>•</sup>]. However, when compared with a MI, myocarditis was significantly more common in patients with troponin elevations who were less than 40 years old [19<sup>•</sup>]. In a recent study of 670 patients with suspected myocarditis, 52% presented with acute chest pain syndromes, 30% with subacute dyspnea and/or left ventricular dysfunction, and 63% had abnormal troponin levels [20<sup>••</sup>]. A recent position statement from the European Society of Cardiology (ESC) suggests that in the absence of significant angiographic coronary artery disease (stenosis  $\geq$ 50%) or preexisting conditions that could explain the clinical scenario, patients who have at least one of five common clinical presentations and/or certain supportive diagnostic testing should be considered as having ‘clinically suspected myocarditis’ and thus warrant further evaluation (Fig. 1) [3].

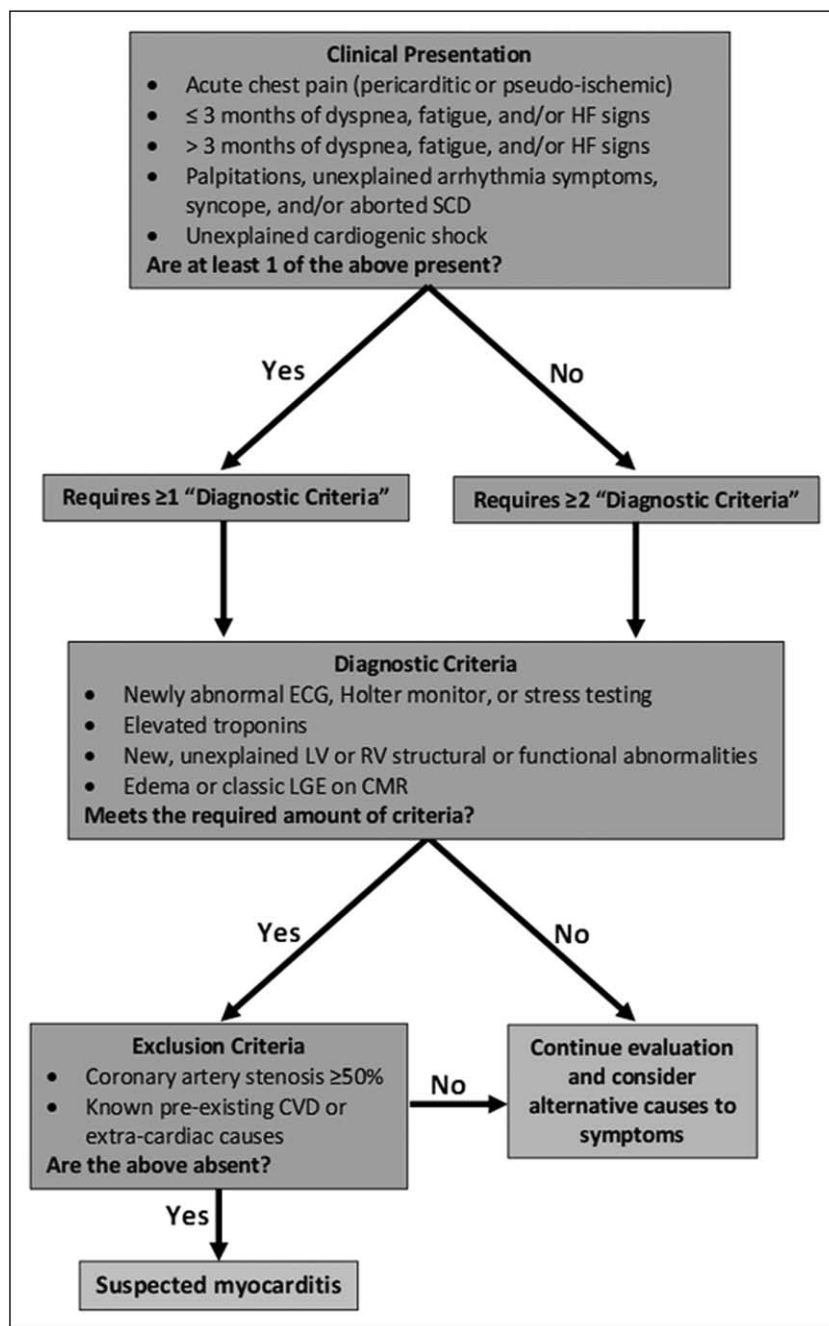
Although ECG, cardiac biomarkers and echocardiography all remain part of the initial evaluation for a patient with suspected myocarditis, individually, they cannot make a diagnosis with absolute certainty, and all lack sensitivity [21]. Although limitations exist with the technical aspect of EMB (e.g. sampling error and low sensitivity) [22] and the utility of the previously established histopathological Dallas criteria have come into question [23], EMB is still supported by the American Heart Association (AHA), American College of Cardiology (ACC) and ESC in certain situations [24]. Also, the ‘revised Dallas criteria’ have been proposed that also incorporate technical procedural aspects, immunohistochemistry and viral genome analysis [3]. However, given that the overall complication rate is low with experienced operators, and EMB may yield

important diagnostic and prognostic information, clinicians should not purposefully avoid the procedure in the appropriate clinical scenario [9<sup>•</sup>,24]. The sensitivity of the EMB increases when immunoperoxidase stains are used to detect CD3-stained T lymphocytes and/or CD68-stained macrophages along with human leukocyte antigen class II antibodies and viral stains [25].

In recent years, cardiac magnetic resonance (CMR) has become a widely used modality in the diagnosis of myocarditis, which has accounted for nearly one-third of the indications in a multinational registry of more than 27 000 patients receiving CMR [26]. Previously, the Lake Louise Consensus Criteria were established to evaluate for myocardial oedema, hyperemia and late gadolinium enhancement (LGE), in making the diagnosis of acute myocarditis [21]. However, the recently published MyoRacer-Trial studied 129 patients with CMR and EMB, comparing T1 and T2 mapping as well as the Lake Louise Criteria (LLC) [27<sup>••</sup>]. The investigators found both T1 and T2 mapping provided superior diagnostic accuracy compared with the LLC for acute ( $\leq$ 14 days) symptoms, while only T2 mapping provided acceptable diagnostic accuracy in patients with chronic ( $>$ 14 days) symptoms [27<sup>••</sup>]. Several studies have shown that the sensitivity and specificity are highest in patients with suspected acute rather than chronic myocarditis [27<sup>••</sup>,28], and among those with acute myocarditis, CMR is more sensitive in patients with chest pain (i.e. ‘infarct-like’) presentations (80%) than cardiomyopathic (57%) and arrhythmic (40%) presentations [29]. Overall, although the diagnosis of myocarditis can usually be made using clinical diagnostic criteria in conjunction with CMR, the role of EMB may be used in patients with heart failure and/or cardiomyopathy, when a diagnostic dilemma remains despite noninvasive testing, or the results of the biopsy are likely to change clinical management. Furthermore, when EMB is indicated, clinicians should consider utilizing a left ventricular biopsy seeing as myocarditis primarily involves the left ventricle (LV), the sensitivity is higher than right ventricle (RV) biopsy, and the complication rates are similarly low (0.33%) with experienced operators [30].

## TREATMENT AND PROGNOSIS

The treatment options and outcomes of patients with myocarditis depends on a number of factors, including the clinical presentation (i.e. fulminant, acute, chronic active or chronic persistent), patient comorbidities and cause. For instance, acute myocarditis generally resolves in nearly 50% of patients



**FIGURE 1.** Proposed algorithm to diagnosis myocarditis. Patients who are asymptomatic require at least two diagnostic criteria to be present, while those who meet at least one of the typical clinical presentations require only one diagnostic criteria to be present. All patients require the exclusion of common disease states such as significant coronary artery disease, valvular heart disease, congenital heart disease and extracardiac diseases that may mimic myocarditis. CMR, cardiac magnetic resonance; CVD, cardiovascular disease; HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle. Adapted from Caforio *et al.* [3].

in 2–4 weeks, nearly 30% of patients will develop DCM and the remaining nearly 20% of patients may deteriorate, require heart transplantation, or die [3]. In a retrospective analysis of patients with clinically suspected myocarditis undergoing EMB, New York Heart Association (NYHA) functional class III or IV,

immunohistological signs of inflammation, lack of beta-blocker therapy, lower ejection fraction [31] and QRS duration at least 120 ms were all associated with higher rates of cardiac death or heart transplantation [32]. Contemporary studies have utilized CMR to provide prognostic information [20<sup>11</sup>,33<sup>11</sup>].

In a large cohort of more than 600 patients undergoing CMR for suspected myocarditis, LGE was strongly associated with higher rates of major adverse cardiovascular events (MACEs) during a median follow-up of 4.7 years [20<sup>\*\*\*</sup>]. Furthermore, the investigators found that patients with LVEF less than 40% had significantly higher annual MACE rates than those with LVEF at least 40%, and the presence of LGE was associated with incrementally higher annual MACE rates in either group. The association of LGE with MACE was strongest among patients with a septal distribution [20<sup>\*\*\*</sup>]. Others have demonstrated that LGE in an anteroseptal distribution, compared with other distribution patterns, was associated with unfavorable outcomes, such as an increased risk of sudden cardiac death and heart failure hospitalization [33<sup>\*\*\*</sup>].

For the subset of patients who develop heart failure and DCM, they should be treated with standard heart failure guideline-directed medical therapy (GDMT) [34]. Data on routine use of prednisone [35] or intravenous immune globulin (IVIG) [36] for idiopathic DCM have not shown significant benefit. However, a small pilot study of 17 patients with high viral loads of Parvovirus B19 and chronic DCM found IVIG administration improved LVEF and NYHA functional class [37], but this finding requires further investigation.

Patients with fulminant myocarditis present with rapid onset of symptoms and severe haemodynamic compromise requiring inotropic and/or mechanical circulatory support (MCS). Historically, patients with fulminant myocarditis, although more sick at presentation, were thought to have better long-term survival [38]. Large cohort data from Taiwan have supported the idea of similar long-term outcomes, but increased cardiovascular death in the first 3 months of diagnosis among fulminant myocarditis patients compared with those with nonfulminant presentations [39<sup>\*</sup>]. Recent data have also supported the notion of worse early outcomes among fulminant myocarditis compared with acute nonfulminant myocarditis [40<sup>\*</sup>]. In a retrospective analysis of 187 patients with acute myocarditis, 29% presented with fulminant myocarditis with an associated 18% in-hospital mortality rate and 25% composite of in-hospital mortality and heart transplant rates, compared with 0% for either endpoint among those with nonfulminant myocarditis [40<sup>\*</sup>]. Notably, the overall improvement in LVEF during hospitalization was greater among patients with fulminant myocarditis, but the absolute LVEF at discharge remained less than those with nonfulminant myocarditis [40<sup>\*</sup>].

Along with appropriate GDMT, when not contraindicated, patients with fulminant myocarditis

require inotropic and/or temporary MCS, and may progress to requiring left ventricular assist device (LVAD) or heart transplant [40<sup>\*</sup>]. One study found that 46% of patients requiring venoarterial extracorporeal membrane oxygenation (VA-ECMO) were able to be successfully decannulated and subsequently discharged from the hospital [41]. The absolute LVEF and change in LVEF were strong predictors of successful VA-ECMO [41]. Consistent with studies in other populations, temporary MCS is associated with higher rates of complications, particularly among ECMO patients, including renal failure, need for haemodialysis, stroke and ventricular arrhythmias [39<sup>\*</sup>]. Although less than 1% of adults listed for heart transplantation in the United States have a diagnosis of myocarditis, the patients are typically younger, more often status 1A and more often required mechanical ventilation, biventricular mechanical support and ECMO [42<sup>\*</sup>]. Although patients with a diagnosis of myocarditis were more likely to be delisted for clinical improvement, those who did receive a transplant had comparable outcomes to other heart transplant recipients [42<sup>\*</sup>].

## CONCLUSION

Myocarditis is a disease with a variety of causes and nonspecific presentations that may range from mild symptoms to life-threatening cardiogenic shock and associated complications. Although EMB remains the gold standard for diagnosis, over the past several decades, the increased use of CMR has allowed for an accurate and noninvasive method to make the diagnosis of myocarditis. A minority of patients will develop a DCM, and the pathogenesis clearly involves an autoimmune process and subsequent sequela. The role of immunomodulators to improve cardiac function and clinical outcomes remains uncertain, and likely limited to specific subsets of patients. Continued investigation into the pathophysiology will allow for identification of potential therapeutic targets. Meanwhile, clinicians should be mindful that while most patients with acute myocarditis have resolution of symptoms, those who present with fulminant myocarditis have worse early outcomes and are at higher risks for treatment-related complications.

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## Conflicts of interest

*The authors have no conflicts of interest to disclose.*

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- of special interest
- of outstanding interest

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