MYOCARDITIS

Relevant Guidelines

ESC 2025 guidelines on myocarditis and pericarditis

2025 ESC Guidelines for the management of myocarditis and pericarditis. *Eur Heart J*. 2025.

ESC 2021 guidelines on heart failure

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J

ESC 2022 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022.

AHA/ACC/HRS 2017 Guideline on ventricular arrhythmias and prevention of sudden cardiac death

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *JACC*. 2017

ESC 2020 Guidelines on sports

Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020.

Relevant Scientific Statements and Position Papers

AHA 2020 Scientific Statement on Fulminant Myocarditis

Recognition and Initial Management of Fulminant Myocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2020:CIR0000000000000745.

ESC, Heart Failure Society of America and Japanese Heart Failure Society 2021 Position statement on endomyocardial biopsy

Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy. *Eur J Heart Fail*. 2021.

AHA 2020 Scientific Statement on SARS-CoV-2 Infection

SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults: A Scientific Statement From the American Heart Association. *Circulation*. 2022:101161CIR0000000000001064.

ACC 2024 Consensus Statement on Myocarditis

2024 ACC expert consensus decision pathway on strategies and criteria for the diagnosis and management of myocarditis: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2025;85:391–431

ESC Groups 2026 Statement on arrhythmias in myocarditis

Workup and management of rhythm disorders in myocarditis and inflammatory cardiomyopathy: a clinical consensus statement of the European Heart Rhythm Association and the Heart Failure Association of the ESC, the ESC Working Group on Myocardial & Pericardial Diseases, the European Association of Preventive Cardiology of the ESC, the Heart Rhythm Society, the Asian Pacific Heart Rhythm Society, and the Latin American Heart Rhythm Society. *Europace*. 2026;28.

ACUTE MYOCARDITIS

Definition and Classification

Myocarditis refers to inflammation of the heart muscle due to exposure to external or self-antigens (Table 1). Diagnosis is currently based on unexplained rise of cardiac troponins, ECG changes suggestive of acute myocardial injury, and noninvasive imaging findings such as cardiac magnetic resonance.[1-4] Pathological confirmation of myocardial inflammation is traditionally required for a definitive diagnosis of myocarditis,[2] but endomyocardial biopsy is subject to sampling error and the conventional Dallas criteria have been abandoned.[5] Immunohistochemical staining for characterization of inflammation and polymerase chain reaction (PCR) for viral genome detection may carry prognostic significance.[6]

Clinicopathological classifications were based on early studies that used myocardial biopsies and conventional histology. Lymphocytic infiltration was the more common finding, usually in myocarditis due to viral, immune or systemic disorders. **Acute lymphocytic myocarditis** does not have a distinct onset and hemodynamic compromise. The mild form has good prognosis but may result in death or the need for cardiac transplantation when presented with symptoms and LVEF<45%.[7,8] **Acute necrotizing eosinophilic myocarditis** is an aggressive form of eosinophilic myocarditis with acute onset and ominous prognosis. [9] It may be seen in association with other disorders, including allergic reactions to drugs, eosinophilic granulomatous polyangiitis (formerly Churg-Strauss syndrome), Loeffler endomyocardial disease, parasite infections, and idiopathic hypereosinophilic syndrome.[10 11] Ulcerative colitis is a previously unrecognized associated cause of eosinophilic myocarditis in ≈5% of patients.[11] **Giant cell myocarditis** is a rare, often rapidly progressive and potentially fatal, disease due to T-cell lymphocyte-mediated inflammation of the myocardium that typically affects young and middle-aged adults.[12] It has an ominous prognosis due to severe heart failure, ventricular tachycardia or block, and patients often need mechanical support and transplantation. It is important to be distinguished from ***cardiac sarcoidosis*** that may present with similar clinical features. Atrial giant cell myocarditis represents a more benign form.[13] We know now that these well-defined conditions are rare and patients without distinct clinical pathological manifestations encompass a much broader category.[5,14]

Fulminant myocarditis is a form of presentation (approximately 8% of myocarditis cases) characterized by sudden and severe diffuse cardiac inflammation often leading to death resulting from cardiogenic shock, ventricular arrhythmias, or multiorgan system failure (Table 2).[15] There is rapid onset of severe heart failure of <2-week symptom duration requiring parenteral inotropic or mechanical circulatory support,[16] but long-term prognosis is

excellent among hospital survivors.[17] Prognosis of fulminant myocarditis is worse with giant cell myocarditis than the eosinophilic and lymphocytic types.[18]

The ESC 2025 guidelines introduced a new category, '**inflammatory myopericardial syndrome (IMPS)**', as an umbrella term to increase understanding of the potential myocarditis–pericarditis overlap (Table 3, and Figures 1 and 2).[4]

Epidemiology

The true incidence of myocarditis is difficult to determine and is basically unknown, but it is estimated to approximately 0.01-0.02%.[1,3] It rises to 0.2% in patients hospitalized for COVID-19 infection.[3] Myocarditis can be the cause of sudden death in 3-10% of adults, and its burden as a percentage of prevalent heart failure varies by age and region from 0.5% to 4%.[1,19] Parvovirus B19-associated acute myocarditis is an increasingly recognized entity in the pediatric population, and was responsible for the 2024 outbreak of PVB19 infections was reported across Europe and the United States.[20]

Aetiology

Several infectious and noninfectious diseases can cause myocarditis.[21,22] Table 1 presents the most common ones. In the western world the most common cause is viral infections. The predominant viral cause of this disease continually changes (***coxsackie in the 1980s, adenovirus in the 1990s, and parvovirus B19 since 2000***).[23-25] PCR analysis of viral genomes in myocardial tissue from endomyocardial biopsy samples has now replaced viral culture and serial serological testing. The most common viruses identified by this method are ***parvovirus B19, H1N1 influenza, adenovirus, coxsakie B, human herpes virus 6, cytomegalovirus, Hepatitis C,*** and ***HIV***. The question whether these viruses are innocent bystanders or pathological agents still remains. ***Desmoplakin*** cardiomyopathy should also be considered in the differential diagnosis for acute myocardial inflammatory syndromes.[26] Autoimmune and systemic diseases may also rarely cause acute myocarditis (7% and up to 15% in patients with a complicated presentation).[27] ***Lupus myocarditis*** can affect approximately 10% of patients with lupus, typically presents with an indolent course, but can present acutely as well. Concomitant systemic lupus erythematosus is also seen in 40% of antiphospholipid antibody syndrome (***APLAS***) patients. APLAS is a disorder of thrombotic events or obstetric complications such as repeated miscarriages in the presence of sustained high titers of antiphospholipid antibodies. A catastrophic form characterized by clotting in multiple vascular beds may also present in the context of acute myocarditis.[28] Myocarditis may rarely occur in patients treated with immune checkpoint inhibitors for cancer, such as ***ipilimumab*** and ***nivolumab***, but fatality rates are high (30-50%).[29,30] Overall, the incidence of clinically suspected myocarditis during acute ***COVID-19*** infection ranges from .01% to

.12%.[31] Acute myocarditis is seen in between 2.4 and 4.1 out of 1000 patients hospitalized for COVID-19. The majority occurs in the absence of pneumonia and is often complicated by hemodynamic instability.[32,33] COVID-19 infection–related ***Multisystem Inflammatory Syndrome*** is a rare but serious hyperimmune response in children and adolescents that occurs ≈4 weeks after acute viral infection. LV dysfunction is the most common cardiac manifestation, followed by coronary artery aneurysm and electric conduction abnormalities.[34,35] Myocarditis has been recognized as a rare complication of ***COVID-19 mRNA vaccinations***, especially in young adult and adolescent males and after a booster dose.[36] The incidence is approximately 4 in 100,000 persons, and most cases (98%) are mild or moderate. Thus, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups.[31,33,35,37-39] ***Parasitic infections*** should be s considered in patients with unexplained myocardial or pericardial disease of uncertain aetiology when epidemiological exposure, systemic features, eosinophilia, or immunosuppression are present.[40] Myocarditis may also occur early after starting treatment with ***immune checkpoint inhibitors*** (novel agents that help target immune responses toward cancer cells), has a malignant course, and responds to higher steroid doses.[41-43]

Necrotizing coronary vasculitis is histologically detectable in 1.5% of myocarditis. ***Infectious agents, auto-reactive mechanisms,*** and ***autoimmune diseases*** are mostly involved, and intra-hospital mortality is 24%.[44] Certain autosomal recessive defects in ***genes*** encoding various components of cardiac structure can predispose to acute myocarditis in young individuals after common viral infections.[45] In a recent series, approximately 8% of patients with acute myocarditis (compared with <1% of healthy controls), variants in a gene robustly linked to dilated cardiomyopathy or arrhythmogenic cardiomyopathy may be found.[46]

Pathophysiology

It is not completely understood. Acute infection results in myocyte death and activation of the innate immune response, including interferon gamma, and mobilization of natural killer cells with phagocytosis of released viral particles and cardiac proteins.[2,47] The immune reaction in the heart causes structural and functional abnormalities in cardiomyocytes, with consequent regional or global contractile impairment, diastolic dysfunction, or conduction system disease. Most patients recover, but a subset has progression to a second phase, consisting of an adaptive immune response. In this response, antibodies to viral proteins, and to some cardiac proteins (including cardiac myosin and β1 or muscarinic receptors), are produced, and effector T cells proliferate. Eventually the immune response is down-regulated, and fibrosis replaces a cellular infiltrate in the myocardium. Under neurohumoral stimulation and hemodynamic stress, the ventricles dilate and may lead to chronic cardiomyopathy.

Presentation

Presentation of disease can vary, ranging from minor symptoms of malaise to acute heart failure. In adults, symptoms of viremia such as fever, myalgias, arthralgias, fatigue, and respiratory or gastrointestinal symptoms frequently, but not always, precede the onset of myocarditis by several days to a few weeks. Patients may present with dyspnea, chest pain, palpitations, and decreased exercise tolerance (Table 4 and Figures 3 and 4). Occasionally, the condition resembles myocardial infarction. Fulminant cases are rare, but children, particularly infants, have a more fulminant presentation than adults. Many kinds of arrhythmias may occur at any stage of the disease.[48] Ventricular arrhythmias are usually polymorphic and irregular during the active inflammatory phase, and monomorphic and regular in healed myocarditis.[49] Patients who present with apparently chronic dilated cardiomyopathy but with new ventricular arrhythmias or second-degree or third degree heart block or who do not have a response to optimal care are more likely to have cardiac sarcoidosis, a granulomatous myocarditis, or, rarely, Chagas or Lyme disease.[14] Diagnosis of ***giant-cell myocarditis*** requires a high index of suspicion given its often rapid and potentially fatal course.[12] Acute ***eosinophilic myocarditis*** can present without peripheral eosinophilia in up to 42.6% of cases.[11] The magnitude of troponin increase, pre-existing thymoma, presence of symptoms, low LVEF, and low QRS voltage were associated with severe cardiomyotoxicity in ***immune checkpoint inhibitors myocarditis***.[50] Myocarditis may also occur concomitantly with other cardiomyopathies such as arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, and amyloidosis, or myocardial infarction.[14] Atrial giant cell myocarditis is a more benign form and patients may present with atrial dilatation.[13]

Physical Examination

Physical examination may be unremarkable. Fever, tachycardia, S3 or S4 gallop, and pulmonary congestion may be present.

Investigations

Diagnostic criteria and steps are presented in Tables 5-7, and Figures 5-10. Age, pH, and histopathological findings may be useful for risk assessment of fulminant myocarditis.[17]

ECG findings are usually nonspecific ST-T changes. Occasionally it may mimic myocardial infarction or display arrhythmias or LBBB. Q waves or new LBBB are ominous prognostic signs.[51]

Echocardiography may show global or segmental hypokinesia with or without pericardial effusion. Patients with fulminant myocarditis usually have small cardiac chambers and thickened walls, whereas in acute myocarditis there is marked left ventricular dilation and

normal wall thickness.[52] Diastolic filling patterns are abnormal in most patients and the presence of right ventricular dysfunction is an ominous prognostic sign. Atrial dilatation with atrial wall thickening may suggest atrial giant cell myocarditis.[13]

Cardiac biomarkers of myocardial injury are elevated in up to 35% patients with myocarditis. Increased serum concentrations of troponin T (TnT) and, especially troponin I (TnI) are more common than increased levels of CK-MB in both adults and children with acute myocarditis.[53] Serum levels of interleukin-10 on admission are a prognostic predictor of human fulminant myocarditis.[47] Routine virology samples are not necessary, but cardiac-specific auto-antibodies should be tested.[54]

Cardiacmagnetic resonance (CMR) with late gadolinium enhancement assessment provides information about tissue necrosis and fibrosis, hyperemia and interstitial edema and is a useful prognostic tool (Table 8).[55-58] The T2-weighted edema imaging is used as a tool for evaluating the presence of acute myocardial inflammation, especially in patients with heart failure in the chronic phase of myocarditis.[59,60] T1-weighted imaging (early gadolinium enhancement-EGE) visualizes hyperaemia and capillary leakage, while myocardial necrosis and fibrosis are detected 10 min after the injection (late gadolinium enhancement-LGE). In patients with acute myocarditis native T1 mapping had superior diagnostic accuracy across all CMR tissue characterization methods.[61]

Endomyocardial biopsy. The usefulness of biopsy is limited by sampling error but is necessary in certain conditions such as suspicion of giant cell, fulminant and eosinophilic myocarditis (Tables 9-11. and Figure 11).[7,12,62-64] Electroanatomic voltage mapping may be useful for guiding myocardial biopsy.[65] There is a reported mortality risk of 0.3% with cardiac biopsy, but in experienced centers rates of complications such as perforation or embolization (but no deaths) have been reported as 0.33% with LV and 0.45% with RV biopsy. [66 67] Perforation is higher with RV biopsy, but TIAs as well as diagnostic yield are higher with LV biopsy (under 1 g IV aspirin).[68] In addition to histologic and immunohistochemical assessment of biopsy specimens, a ***polymerase-chain-reaction*** assay or in situ hybridization is recommended to screen for viruses, even though the clinical significance of viral infection
and the causal link between such infection and cardiac injury are still under investigation.[3]

Myocardial gene expression profiling is a novel method that has been proposed to predict the presence of multinuclear giant cells in the myocardium in single biopsy sections even without a direct histological proof, and thus to reduce the risk of sampling errors.[69] If established, it could be of particular help to distinguish between giant cell myocarditis and cardiac sarcoidosis.

PET scanning may be useful (Table 12).

Plasma polymerase chain reaction for PVB19 testing should be incorporated into the diagnostic workup of pediatric myocarditis.[20]

Genetic testing. Genetic sequencing is indicated in patients presenting with acute myocarditis, since genotype-positive individuals for dilated or arrhythmogenic cardiomyopathy may remain phenotypically silent until the occurrence of an environmental trigger (Table13 and Figure 12).[46]

Autopsy is indicated when an inherited cause is suspected (Table 14).

Therapy

In patients with high-risk/complicated inflammatory myopericardial syndrome, a multidisciplinary team discussion at a referral centre is recommended to provide a patient-tailored approach (ESC 2025 GL on myocarditis and pericarditis, I C).[4] Because of the high incidence of LV dysfunction, standard therapy for heart failure is administered. ***Beta-blocker*** treatment should be avoided in the acute phase of decompensated heart failure and in the very early treatment of fulminant myocarditis (Table 15 and Figure 13).[70] In patients with suspected myocarditis, the lack of beta-blocker treatment is associated with poor outcome.[6] Digitalis is contraindicated, whereas dihydropyridines may be beneficial but not in acute heart failure.[47] In animal studies NSAIDs have increased inflammation and mortality, and should be given at the lowest required dose in patients with perimyocarditis in whom LV function is clearly normal and have prominent chest pain from pericarditis.[70] Specific therapy depends on the presence or absence of viral infection and active inflammation (Tables 16-18).

Immunosuppression with ***steroids*** and ***azathioprine*** for 3-6 months has been found effective in patients with chronic dilated cardiomyopathy, and biopsy-proven, virus-negative myocarditis, [71-74] in HLA upregulation on biopsy,[75] and in giant-cell myocarditis.[12] It may also be useful in giant-cell myocarditis, esosinophilic myocarditis, and sarcoidosis, and necrotizing coronary vasculitis.[11,44,70,76] Of note, immunosuppression as a routine therapy has not proved useful in patients with acute myocarditis and reduced LV function in the past.[8]

Viral genome analysis of endomyocardial biopsies suggests that up to 70% of chronic DCM patients may carry one or more cardiotropic viruses, and patients with virus replication may benefit from ***intravenous immune globulin (IVIG).***[1] In recent onset dilated cardiomyopathy or myocarditis ***intravenous immune globulin*** did not improve LV function.[77] However, in children with acute myocarditis, high dose gamma-globulin (2 g/kg, over 24 hours) resulted in improvement of LV function and a tendency to better survival in the first year after treatment.[78] ***Interferon*** has also resulted in the elimination of the viral genomes and improved left ventricular function in patients with chronic dilated cardiomyopathy and persistent viral genomes.[79]

High-grade AV block in acute lymphocytic myocarditis may be temporary, but ICD implantation may be indicated in patients with giant cell myocarditis, regardless of LVEF.[80,81] Recommendations on ***arrhythmia*** management are provided in Table 19 and Figure 14. During active inflammation, antiarrhythmic therapy is combined with aetiology-targeted treatment or immunosuppression when indicated.[82]

In fulminant myocarditis, prolonged *circulatory support* may provide benefits beyond its primary function of mechanical circulatory support in the form of additional disease-altering effects, which may contribute to enhanced myocardial recovery/remission (Table 20).[83,84]

Inflammatory cardiomyopathy is defined by chronic myocarditis in association with cardiac dysfunction and ventricular remodelling, with a clinical hypokinetic phenotype, either dilated or non-dilated, with or without arrhythmogenic substrate (Figure 21).[84]

Physical activity is avoided in the acute phase (Table 22 and Figurec15).[85,86] Follow u is presented in Table 23.

Prognosis

Recent data indicate an overall 11% mortality on appropriate medical therapy and haemodynamic support when indicated.[87] Up to 20% of myocarditis patients may subsequently develop a chronic inflammatory dilated cardiomyopathy.[73] Both LVEF and left atrial size at presentation and at 6-month re-evaluation carry prognostic significance.[88] Presentation with heart failure and LVEF<45% carries a bad prognosis with mortality 50% at 4 years. NYHA class, immunohistological signs of inflammation, and lack of beta-blocker therapy, but not histology (positive Dallas criteria) or viral genome detection, have been related to poor outcome within the next 5 years.[6] The presence of late gadolinium enhancement on cardiac MRI has been found the best independent predictor or mortality in biopsy-proven viral myocarditis.[55] Patients presenting with LGE in the midwall of the anteroseptal myocardial segments had a worse prognosis than did patients with other patterns of distribution.[56] Patients with a normal CMR study have a favorable outcome.[57] However, results from the recent Multicenter Lombardy Registry indicate that overall serious adverse events and the risk of subsequent cardiomyopathy after acute myocarditis are lower than previously reported in patients with an LVEF and no ventricular arrhythmias, despite evidence of increased necrosis biomarkers and late gadolinium enhancement at cardiac magnetic resonance.[27] Viral persistence in the myocardium has also been associated with progressive cardiac dysfunction, [23,25] and biopsy-proven myocarditis is associated with a 19% mortality over the next 4.7 years.[55] Patients with fulminant viral myocarditis with severe

hemodynamic compromise had been reported to have a favorable long-term prognosis and, under aggressive hemodynamic support,[89] to be more likely to experience complete recovery than patients with acute (non-fulminant) myocarditis.[90] More recent data indicate a worse prognosis of fulminant compared to non-fulminant myocarditis.[16] In a meta-regression analysis, high grade AV block, major arrhythmic events at presentation, and fulminant myocarditis were associated with higher risk of major arrhythmic events during follow-up, while male gender resulted as a protective factor.[87]

In patients with cardiac sarcoidosis or giant cell myocarditis, prognosis depends probably on an early initiated treatment (immunosuppressive therapy or heart transplantation).

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