REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Myocarditis

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According to the 1995 World Health Organization Task Force on cardiomyopathies, myocarditis is an inflammatory disease of the myocardium that is diagnosed on the basis of established histologic, immunologic, and immunohistochemical criteria.[1] Since the introduction of the Dallas criteria in 1987,[2] endomyocardial biopsy has been considered the standard method of diagnosis.[3-7] Over the past two decades, however, the diagnostic workup has changed with the introduction of new tools, mainly highly sensitive troponin and cardiac magnetic resonance imaging (MRI)[8,9]; in routine clinical practice, a combination of symptoms and signs, laboratory testing, and imaging studies is often sufficient to establish the diagnosis.

The definition and diagnosis of myocarditis vary widely. For myocarditis associated with coronavirus disease 2019 (Covid-19) or with Covid-19 vaccination, the diagnostic criteria have been adapted from those established by the Centers for Disease Control and Prevention and the Brighton Collaboration.[10,11]

## Epidemiology

Before the Covid-19 pandemic, the estimated global incidence of myocarditis was 1 to 10 cases per 100,000 persons per year.[12] The highest risk was among people between 20 and 40 years of age and among men. In the 35-to-39-year-old age group, the rate was 6.1 cases per 100,000 men and 4.4 cases per 100,000 women, with similar rates in the 20-to-44-year-old age group.[13] The increased use of cardiac MRI has led to a gradual rise in the reported incidence of myocarditis in the United States, from 9.5 to 14.4 cases per 100,000 persons.[14]

Precise data on the burden of myocarditis are available only for selected clinical settings. For instance, the incidence of myocarditis among patients with heart failure varies from 0.5% to 4.0% according to age and region.[15] Among patients with chest pain who were seen in the emergency department, 3% had acute myocarditis and pericarditis.[16] A diagnosis of myocarditis was made on the basis of cardiac MRI in one third of patients with a previous diagnosis of acute myocardial infarction and nonobstructed coronary arteries.[17] Autopsy studies in young people who died suddenly have shown a variable incidence of myocarditis. The incidence was 12% in the prospective registry of northeastern Italy.[18] Among patients with advanced cancers who were treated with immune checkpoint inhibitors, the incidence was 1.14%.[19] During the Covid-19 pandemic, 2.4 cases of definite or probable myocarditis and 4.1 cases of definite, probable, or possible myocarditis have been reported per 1000 patients hospitalized for Covid-19.[20] Finally, analysis of currently available data on Covid-19 messenger RNA (mRNA) vaccine related myocarditis suggests an overall incidence of 0.3 to 5.0 cases per 100,000 people in the United States and Israel.[21-24] The Food and Drug Administration and the European Medicines Agency have recently estimated that the risk of

myocarditis is about 1 case in 100,000 people vaccinated against Covid-19, with a higher risk among young males.[25]

## CAUSES AND PATHOGENESIS

Myocarditis can result from a wide range of infectious or noninfectious causes, such as viruses, immune-system activation (autoimmunity [e.g., in sarcoidosis] or immune stimulation [e.g., vaccines or cancer therapies]), or exposure to toxins and drugs, including endogenous biochemical compounds, as seen in amyloidosis and in thyrotoxicosis. Among infectious forms of myocarditis, viruses are the most common cause. In selected populations, however, infections with nonviral pathogens (e.g., bacteria [*Corynebacterium diphtheriae* and *Borrelia burgdorferi*] and parasites [*Trypanosoma cruzi*]) and poststreptococcal autoimmune rheumatic carditis are still major causes.[26]

Data on the real prevalence of viral myocarditis are not available, since endomyocardial biopsy and viral genome searches are rarely performed in routine practice. Seasonal, geographic, and socioeconomic differences and different attitudes toward vaccination must also be considered. Virus-mediated myocarditis can be due to primary cardiotropic viruses, such as adenoviruses and enteroviruses (e.g., coxsackievirus), vasculotropic viruses (e.g., parvovirus B19 [PVB19]), lymphotropic viruses (e.g., cytomegalovirus, Epstein Barr virus, and herpesvirus 6 [HHV-6]), cardiotoxic viruses (e.g., hepatitis C virus, human immunodeficiency virus [HIV], and influenza virus), and possibly angiotensin-converting enzyme 2 tropic cardiotoxic viruses (e.g., coronaviruses, including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).[26] An epidemiologic shift from traditional cardiotropic viruses to PVB19 and HHV-6 has become apparent in the past 30 years.[27] However, since PVB19 and HHV-6 can also be seen in normal hearts or in association with other diseases (innocent bystanders), a viral DNA copy number that exceeds a threshold of 500 copies per microgram has been proposed for establishing a virus as the cause of myocarditis.[28,29]

Our understanding of the pathophysiology of viral myocarditis is mainly derived from experimental murine studies of cardiotropic viruses, with three temporal phases: viral entry into cardiac myocytes through a transmembrane receptor, with necrosis, apoptosis, and activation of innate immunity (1 to 7 days); viral replication and activation of acquired immune responses, with T-cell infiltration and autoantibodies (1 to 4 weeks); and either viral clearance or evolution toward dilated cardiomyopathy (months to years).[30] Whether other, nonprimary cardiotropic viruses cause direct tissue damage or act as triggers for immune-mediated damage is still uncertain; the latter mechanism is probably involved in myocarditis associated with SARS-CoV-2 and other respiratory viruses.[20,31] Furthermore, the pathways that determine the transition from myocardial inflammation to chronic ventricular dysfunction are not fully elucidated, and it is not clear why some patients recover and others do not.

In the context of Covid-19, the mechanisms of cardiac injury are likely to be multifactorial and may include not only endothelialitis or myocarditis but also myocardial injury due to a mismatch between oxygen supply and demand, microvascular thrombosis, a systemic hyperinflammatory response, and myocardial ischemia.[32]

Multiple pharmacologic agents have been associated with myocarditis, mainly antipsychotic agents, cytotoxic drugs, immunotherapies, vaccines, and salicylates.[33] A sharp increase in vaccine-related myocarditis was reported in 2010, mainly related to smallpox, anthrax, and influenza vaccines.[33] Vaccine-induced myocarditis is often an eosinophilic myocarditis, as has been shown for myocarditis associated with the smallpox vaccine. More recently, myocarditis has been recognized as a rare complication of Covid-19 mRNA vaccinations.[21-25] A temporal association does not necessarily suggest that the vaccine is the sole cause. Myocarditis could be due to promotion, reactivation, or acceleration of naturally occurring myocarditis through viral or immune-mediated mechanisms.

Immune checkpoint inhibitor therapy represents a new approach to the treatment of advanced cancers in which antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), or programmed death ligand 1 (PD-L1) are used to enhance the T-cell mediated immune response against tumor cells. However, systemic immune-mediated

adverse events, including potentially life-threatening myocarditis, have been increasingly recognized, particularly with the use of combination immune checkpoint inhibitor therapy.[19,34,35]

The role of genetics as a contributing factor in myocarditis is now documented, with putatively deleterious variants in genes related to cardiomyocyte structure and function detected in up to 16% of cases.[36] According to the two-hit hypothesis, the genetic substrate may play a critical role in the phenotypic outcome among patients exposed to infective or toxic factors. Patients with pathogenic gene variants associated with inherited cardiomyopathies seldom present with clinical and histopathological features of myocarditis.[37,38] Gene testing could be considered in all familial forms of myocarditis, not just in familial cardiomyopathy.

The gut microbiome has recently been identified as a potential risk-modifying factor in myocarditis. Mimetic peptides from commensal bacteria may promote inflammatory cardiomyopathy in genetically susceptible persons.[39]

## CLINICAL PRESENTATION

Myocarditis has a variety of clinical manifestations according to the degree of organ involvement[5,31] (Figs. 1, 2, and 3). The main clinical manifestations are chest pain with an otherwise uncomplicated clinical picture (preserved left ventricular ejection fraction [LVEF] and no ventricular arrhythmias), new or worsening heart failure, chronic heart failure, life-threatening hemodynamic compromise (i.e., fulminant myocarditis, with cardiogenic shock and severely impaired left ventricular function), and life-threatening arrhythmia or conduction disturbances (e.g., sustained ventricular arrhythmias, atrioventricular block, and sudden death).

In the past, the diagnosis of myocarditis was based on endomyocardial biopsy, which was performed mostly in patients at moderate or high risk for complications. New tools allowing for a noninvasive diagnosis led to the identification of a wider population of patients with clinically suspected myocarditis, including those with a more favorable prognosis.[31]

Although arrhythmias or conduction disturbances may occur at any stage, patients presenting with conduction abnormalities as the first manifestation of myocarditis[40-42] have not been independently evaluated in international referral studies. A precise correlation between the characteristics of ventricular arrhythmias and the stage of myocarditis has been reported, with irregular, polymorphic ventricular arrhythmias in active myocarditis and regular, monomorphic arrhythmias in chronic myocarditis.[41,42]

The clinical presentation can be a predictor of the outcome. Patients with reduced LVEF, heart failure, advanced atrioventricular block, sustained ventricular arrhythmias, or cardiogenic shock are at increased risk for death or heart transplantation.[43-45] An analysis of data from a collaborative registry of cases of acute myocarditis showed that most patients had an uncomplicated course, with chest pain in 97% of patients and ST-segment elevation on electrocardiography (ECG) in 62%, with no deaths or transplantations at 5 years.[43] Heart transplantation or death from cardiac causes occurred almost exclusively in patients presenting with an LVEF of less than 50%, sustained ventricular arrhythmias, hemodynamic instability on admission, or a combination of these findings (rate of death or transplantation, 10.4% at 30 days and 14.7% at 5 years).[43] Analysis of data from a multicenter registry of endomyocardial biopsy confirmed acute myocarditis with systolic dysfunction (LVEF, <50%) showed the prognostic effect of hemodynamic compromise at presentation, with a 27.8% rate of death or transplantation at 60 days among patients with cardiogenic shock, as compared with 1.8% among those without shock. The prognostic significance of the histologic characterization of inflammation was also confirmed, with giant-cell myocarditis carrying the highest risk.[46]

Giant-cell myocarditis should always be suspected in patients presenting with rapidly progressive heart failure or cardiogenic shock, with or without conduction disturbances, that does not respond to usual therapy. The prognosis is poor, with an 85% rate of death or transplantation at 3 years.[47-49] However, early diagnosis and prompt initiation of aggressive immunosuppressive therapy or advanced mechanical support may reduce the risk of death or need for transplantation.[49,50]

The rate of death or transplantation among patients with eosinophilic myocarditis and a fulminant presentation is more than 26% at 60 days.[46] The use of glucocorticoids has been shown to reduce in-hospital mortality, but data from randomized trials are lacking.[51]

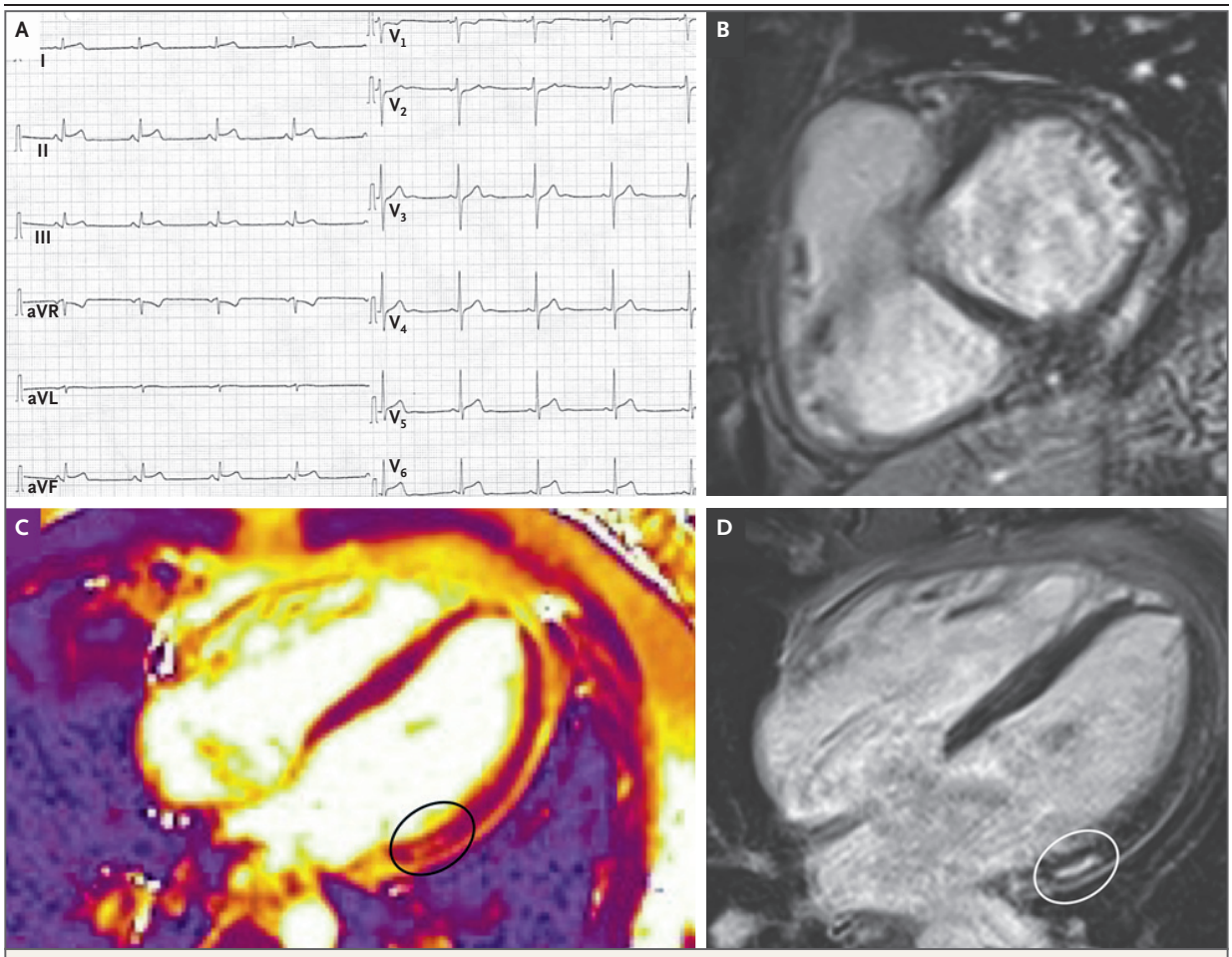


**Figure 1. Infarct-like Presentation with Preserved Left Ventricular Ejection Fraction (LVEF) in an 18-Year-Old Man with Chest Pain and Gastroenteritis.**

A basal 12-lead electrocardiogram (ECG) obtained at admission shows an ST-segment elevation in the inferior leads (Panel A). A cardiac MRI scan shows late gadolinium enhancement with a noncoronary pattern in the orthogonal short-axis view (T1-weighted inversion recovery) (Panel B). A four-chamber view shows myocardial edema as a midwall stria on T2 mapping (Panel C, encircled). Late gadolinium enhancement, with a noncoronary pattern in the same region as the stria in Panel C, is evident on a four-chamber view (T1-weighted inversion recovery) (Panel D, encircled).

Patients who have cardiac sarcoidosis may present with conduction abnormalities and heart failure. Such patients are considered to be at risk for sudden death and may require an implantable cardioverter defibrillator.[52] Studies have shown that up to 35% of patients with complete atrioventricular block who are younger than 60 years of age and 28% of patients with ventricular tachycardia of unknown cause may have undiagnosed cardiac sarcoidosis.[53,54]

### MYOCARDITIS ASSOCIATED WITH COVID-19

Myocarditis is uncommon, but a fulminant presentation is reported in 38.9% of patients with a definite or probable diagnosis.[20] Hemodynamic instability, a need for temporary mechanical circulatory support, and death are more likely in patients with concomitant pneumonia than in those without pneumonia.

### MYOCARDITIS ASSOCIATED WITH COVID-19 VACCINES

Analyses of retrospective data in large populations have shown that after eligible persons have received the mRNA vaccine BNT162b2 (Pfizer BioNTech), myocarditis is very rare, is most common in young men and within a few days after the second dose, and is usually self-limited.[21,22,55]

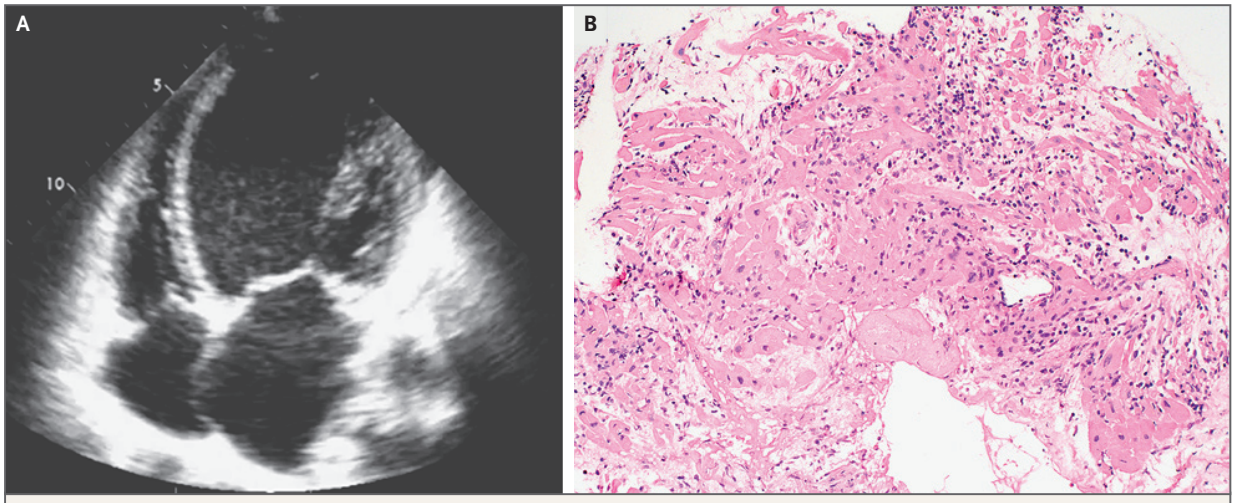


**Figure 2. Cardiogenic Shock with Severely Depressed LVEF in a 48-Year-Old Man with Dyspnea and Hypotension.**

In Panel A, a two-dimensional echocardiogram, four-chamber view, obtained in the intensive care unit (ICU), shows a severely dilated left ventricular chamber with depressed LVEF. In Panel B, an endomyocardial biopsy specimen shows diffuse lymphocytic myocarditis (hematoxylin and eosin). A viral genome search with polymerase-chain-reaction (PCR) and reverse-transcriptase PCR analysis was negative.

More recently, on the basis of passive surveillance reporting in the United States, an increased risk of myocarditis after receipt of an mRNA-based Covid-19 vaccine (e.g., BNT162b2 or mRNA-1273 [Moderna]) was reported across multiple age and sex strata and was highest after the second vaccine dose in adolescent boys and young men.[56] In 87% of the cases, the presenting symptoms had resolved by the time of hospital discharge.

### MYOCARDITIS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY

Analysis of data from the largest series of patients with immune checkpoint inhibitor related myocarditis showed an early onset of symptoms (median interval after the initiation of therapy, 34 days) and high mortality (50%).[57] With the growing awareness of this complication, as well as the increasing number of patients receiving combination immune checkpoint inhibitor therapy, ECG and troponin measurement at baseline and weekly in the first 6 weeks of treatment have been recommended,[31] although there is no clear evidence of the efficacy or value of these routine baseline or serial assessments.[35]

## DIAGNOSIS

The diagnosis of myocarditis relies on multiple sources of data. According to the European Society of Cardiology (ESC) task force,[5] a noninvasive diagnostic workup helps to establish a diagnosis of clinically suspected myocarditis, on the basis of the clinical presentation and criteria in four categories: laboratory testing; electrocardiography, Holter monitoring, and stress testing; functional and structural assessment on cardiac imaging (echocardiography, angiography, and MRI); and tissue characterization on cardiac MRI. Although the ESC recommends selective coronary angiography and endomyocardial biopsy in all patients who meet the diagnostic criteria for clinically suspected myocarditis,[5] recommendations for endomyocardial biopsy vary in the scientific community.[3,6,31] The 2007 American Heart Association (AHA) American College of Cardiology (ACC) ESC report provided the original recommendations on the role of endomyocardial biopsy in various clinical scenarios.[3] More recently, a risk-based approach to the use of endomyocardial biopsy has been proposed on the basis of expert consensus (Fig. 4).[31]

Endomyocardial biopsy can be reserved for patients with clinically suspected myocarditis and the following findings: cardiogenic shock or acute heart failure requiring inotropic or mechanical circulatory support; ventricular arrhythmias or Mobitz type II second-degree or higher atrioventricular block, particularly when symptom onset is recent, with mild or no left ventricular dilatation; peripheral eosinophilia or an

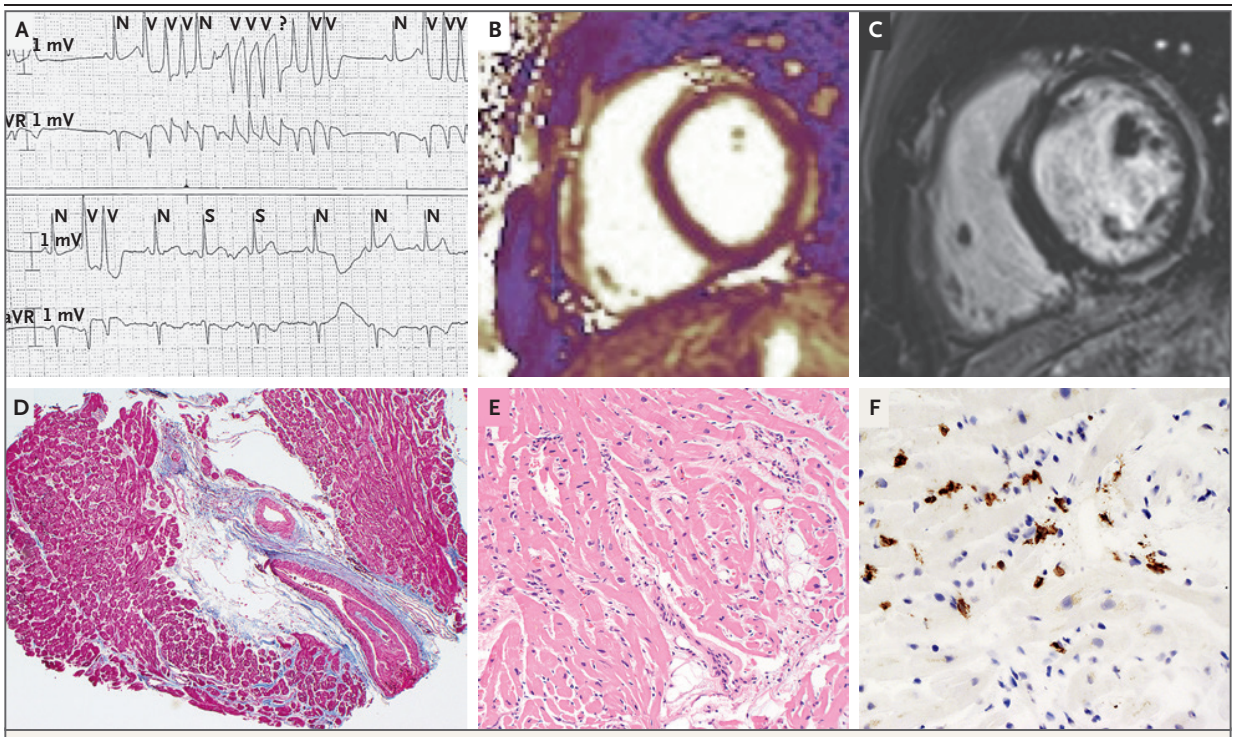


**Figure 3. Refractory Ventricular Arrhythmias and Preserved LVEF in a 42-Year-Old Woman with Syncope.**

An ECG obtained during monitoring in the ICU shows nonsustained ventricular tachycardia (Panel A). N denotes normal QRS complex, S supraventricular premature beat, and V ventricular premature beat. Coronary disease was ruled out on angiography. A cardiac MRI scan shows no evidence of myocardial edema on T2 mapping (short-axis view) (Panel B). A cardiac MRI scan obtained after the administration of contrast material shows epicardial and midmural late gadolinium enhancement, with a noncoronary pattern (short-axis view) (Panel C). Mild focal, replacement-type fibrosis is present (blue) in an endomyocardial biopsy specimen (trichrome stain) (Panel D). Interstitial edema and scarce inflammatory cells are also visible (hematoxylin and eosin) (Panel E). Immunohistochemical staining with CD3 antibody reveals the presence of CD3-positive T lymphocytes (>7 per square millimeter), a finding that is consistent with chronic active myocarditis (Panel F).

associated systemic inflammatory disorder; persistent or recurrent release of necrosis markers, particularly when an autoimmune condition is likely or ventricular arrhythmias and high-degree atrioventricular block are present; or cardiac dysfunction in a patient receiving immune checkpoint inhibitor therapy. In other clinical scenarios, cardiac MRI should be considered as the initial diagnostic test to detect inflammation, and endomyocardial biopsy may be considered on a case-by-case basis, according to the likelihood of detecting a treatable disorder.

### CARDIAC MRI

In cases of clinically suspected myocarditis, cardiac MRI is a valuable tool and has the highest sensitivity if performed within 2 to 3 weeks after the initial clinical presentation. Cardiac MRI is also useful as a follow-up assessment after 6 to 12 months to monitor the evolution of the disease. The 2009 consensus conference on cardiac MRI for the diagnosis of myocarditis identified the following markers (known as the Lake Louise criteria): an intense signal on imaging shortly after gadolinium enhancement, indicating hyperemia; an increased myocardial T2 relaxation time or increased signal intensity on T2-weighted images, reflecting tissue edema; and late gadolinium enhancement, indicating necrosis or fibrosis.[8] These criteria were updated in 2018,[9] with the addition of T2 mapping to detect myocardial edema and increases in native T1-weighted signal intensity and extracellular volume as markers of myocardial injury. The sensitivity and specificity of the original criteria were 74% and 86%, respectively, as compared with 88% and 96%, respectively, with the updated criteria.[58]

The type of inflammation is not identifiable

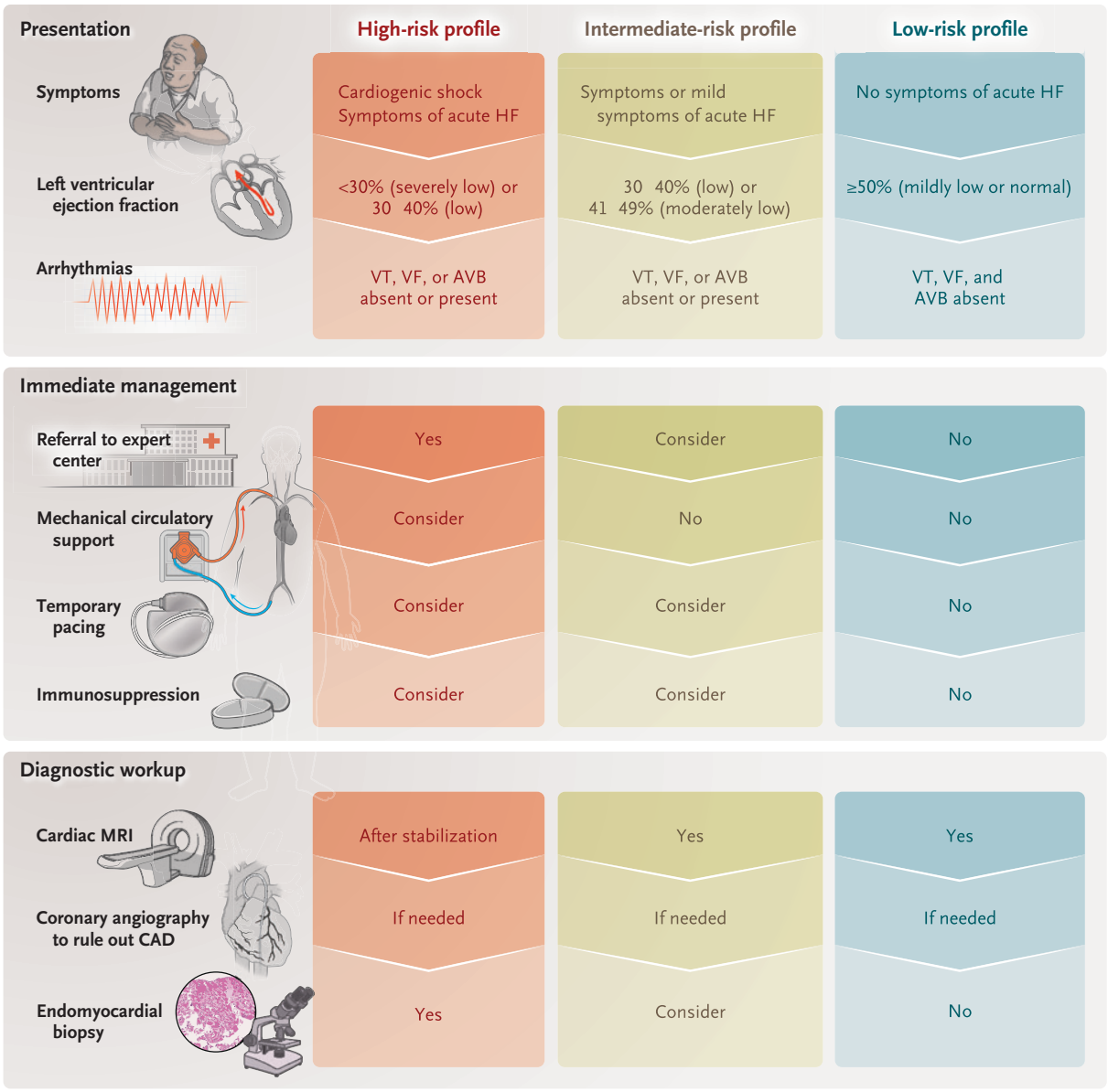


**Figure 4. Risk-Based Approach to Immediate Management and Diagnostic Workup for Clinically Suspected Myocarditis.**

The information is modified from Ammirati et al.[31] Patients with low-risk acute myocarditis should be admitted to the hospital for cardiac MRI based diagnosis and treatment of symptoms. Patients with acute myocarditis with high-risk features require admission to centers that have expertise in endomyocardial biopsy based diagnosis, where they should be considered for mechanical circulatory support and immunosuppression. AVB denotes atrioventricular block, CAD coronary artery disease, HF heart failure, VF ventricular fibrillation, and VT ventricular tachycardia.

on cardiac MRI, although the regional distribution can be a red flag, such as involvement of the basal septum in sarcoidosis. Cardiac MRI features have also been used for risk stratification, since a negative MRI scan in a patient with clinically suspected myocarditis is associated with a good prognosis.[59,60] In contrast, late gadolinium enhancement in the midlayer of the septum and a low LVEF at baseline have been identified as the strongest predictors of an

unfavorable outcome. The persistence of late gadolinium enhancement and the disappearance of edema on follow-up imaging are negative predictors, as compared not only with complete resolution but also with the persistence of both late gadolinium enhancement and edema, probably because the latter findings indicate a process that is still active, with the potential for recovery.[59]

### ENDOMYOCARDIAL BIOPSY

Myocarditis is diagnosed when histologic assessment of a specimen from an endomyocardial biopsy reveals an inflammatory infiltrate, with necrosis or degeneration of adjacent myocytes.[2,4,7] Subtypes can be identified, such as lymphocytic, eosinophilic, and giant-cell myocarditis and cardiac sarcoidosis, which have specific prognostic and therapeutic implications[7,61] (Fig. 5). The presence and extent of fibrosis should also be reported and described as interstitial, endocardial, or replacement-type fibrosis. The availability of immunohistochemical staining to characterize inflammatory cells has led to an increase in positive findings on endomyocardial biopsy.[4,7] Quantitative criteria for inflammation were specified in the 2013 ESC report,[5] but they have not been validated in any population of persons with non-European ancestry. The diagnostic yield of endomyocardial biopsy is highest if the biopsy is performed within 2 weeks after the onset of symptoms. Sensitivity may increase by increasing the number of specimens and by guiding the endomyocardial biopsy through imaging or electroanatomical mapping.[4,40-42]

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.[4,5,7] Standardization of methods for viral genome identification and quantification is needed.[26] The presence of the viral genome in the absence of inflammatory cells is not diagnostic of myocarditis.

### OTHER TESTS

Markers of myocyte injury and inflammation such as the erythrocyte sedimentation rate and C-reactive protein level are usually assessed, al-

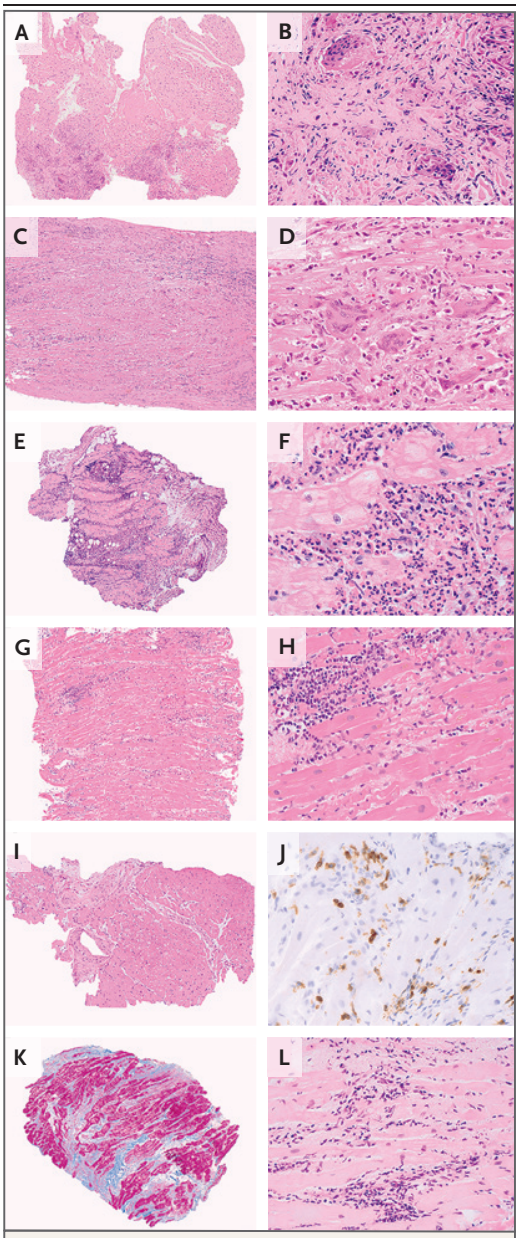


**Figure 5. Histologic Types of Myocarditis Diagnosed by Means of Endomyocardial Biopsy.**

Shown with hematoxylin and eosin staining are histologic samples of cardiac sarcoidosis (Panel A, with a close-up view in Panel B), giant-cell myocarditis (Panel C, with a close-up view in Panel D), eosinophilic myocarditis (Panel E, with a close-up view in Panel F), lymphocytic diffuse myocarditis (Panel G, with a close-up view in Panel H), and lymphocytic focal myocarditis (Panel I, with a close-up view in Panel J [CD3 antibody]). Trichrome staining of a histologic sample shows chronic active myocarditis (Panel K, with a close-up view in Panel L [hematoxylin and eosin]).

though they are not specific and not necessarily increased in myocarditis.[5,31] Troponin is a more sensitive marker than creatine kinase (creatine kinase and creatine kinase MB),[5] but an elevated creatine kinase level could suggest the association of myocarditis with skeletal myositis. A high-sensitivity troponin assay is a valuable tool that can detect myocarditis more accurately than a conventional troponin test.[62] Measurement of brain natriuretic peptides, such as N-terminal pro B-type natriuretic peptide (NT-proBNP), can also be useful but is not specific, and normal results do not rule out myocarditis.[5]

Screening for autoimmune disease is recommended in patients with clinically suspected myocarditis. Routine viral serologic testing is not indicated, since a positive test does not suggest myocardial infection but indicates only the interaction of the peripheral immune system with an infectious agent.[5] There are a few exceptions, such as suspected hepatitis C and rickettsial, HIV, *B. burgdorferi*, and *T. cruzi* infections. Serum cardiac autoantibodies could be evaluated, but such an assessment requires special expertise, and validated cardiac autoantibody tests are not commercially available.[5,31]

MicroRNA profiling in blood and endomyocardial biopsy samples and transcriptome-based biomarkers in endomyocardial biopsy samples have been investigated, with promising results, but correlation between levels in tissue and blood is lacking.[26,63,64] A recent study showed that a novel circulating RNA synthesized by type 17 helper T cells (hsa-Chr8:96) could be used to distinguish patients with myocarditis from patients with myocardial infarction and healthy controls.[65] These data need to be evaluated in other conditions before clinical translation is feasible.

## THERAPY

Treatment for myocarditis comprises management of arrhythmias and heart failure according to conventional guidelines and cause-targeted therapy.[5,31,53,66-68]

### CONVENTIONAL THERAPY

Patients with hemodynamically stable heart failure should be treated with diuretic agents, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockade and beta-adrenergic blockade. Additional treatment with aldosterone antagonists should be considered in patients with persistent heart failure despite adequate management. Whether early initiation of treatment should also be offered to patients with preserved LVEF in order to reduce inflammation, remodeling, and scarring remains uncertain.

Patients with hemodynamically unstable heart failure require inotropic agents. Treatment should be provided in an intensive care unit with respiratory and mechanical cardiopulmonary support facilities, and referral to a tertiary care center should be considered. In patients with cardiogenic shock who present with severe ventricular dysfunction that is refractory to medical therapy, mechanical circulatory support with ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be needed.[46,69,70]

Since myocarditis can be a reversible disease, the main goals of treatment are biventricular unloading, adequate systemic and coronary perfusion, and venous decongestion, in an effort to prevent multiorgan dysfunction and provide a bridge to recovery, transplantation, or use of a durable assist device. Temporary devices, such as an intraaortic balloon pump, venoarterial ECMO, a rotary pump, or an intraaortic axial pump, should be considered. The use of devices that reduce left ventricular afterload, such as a centrifugal or an intraaortic axial pump, alone or in combination with ECMO, is more likely to promote myocardial recovery than ECMO alone.[71] In recent years, left ventricular unloading through a transcutaneously placed axial flow pump (Impella; Abiomed) has been shown to be a viable treatment option for patients with cardiogenic shock, both as the sole left ventricular support when right ventricular function is preserved and in combination with extracorporeal life support or with a right-sided Impella pump. In the absence of protocols for temporary mechanical circulatory support, the choice of device depends on local experience and on right ventricular function.[71] If the patient cannot be weaned from mechanical circulatory support after 2 to 3 weeks, a durable left ventricular assist device or transplantation should be considered.[31]

There are no specific recommendations for the treatment of arrhythmias and conduction disturbances in patients with myocarditis. After

the acute phase, management should be in line with current guidelines on arrhythmia and device implantation.[52,68] Since myocarditis is potentially reversible, a step-by-step approach is suggested during the acute phase. Pacing may be needed for complete atrioventricular block. Use of an implantable cardioverter defibrillator should be deferred until the acute episode has resolved, generally 3 to 6 months after the initiation of the acute phase, and a wearable cardioverter defibrillator can be considered as a bridge.

In competitive athletes, physical activity should be restricted during the acute phase of myocarditis and for a period of 3 to 6 months subsequently, according to the clinical severity and duration of the acute phase.[72,73] After resolution, clinical reassessment is indicated before the athlete resumes competitive sport. Preparticipation screening should be performed every 6 months during follow-up.[5]

#### CONDITION-SPECIFIC THERAPY

Once the treatable causes of eosinophilia such as drugs and parasites have been ruled out, early administration of immunosuppressive drugs (i.e., glucocorticoids alone or together with azathioprine, cyclosporine, or both) is the key therapy for eosinophilic myocarditis, as well as for giant-cell myocarditis and cardiac sarcoidosis.[51,54,74] No specific therapy is available for lymphocytic acute myocarditis, except for the forms associated with systemic diseases and immune checkpoint inhibitors.[5,75]

Although there is a rationale for immunosuppressive therapy in the acute phase of high-risk myocarditis, no data are yet available from prospective trials. The early Myocarditis Treatment Trial showed no benefit of immunosuppression in patients with endomyocardial biopsy proven myocarditis, although the cause was unspecified and the initiation of therapy after disease onset was delayed.[76] Some studies of treatment with prednisone and azathioprine showed favorable results in patients with endomyocardial biopsy proven, virus-negative, chronic inflammatory cardiomyopathy, with an improvement in LVEF.[77-79]

For the safe use of immunosuppressive treatment, the ESC guidelines recommend viral genome analysis on endomyocardial biopsy samples.[5] The recent AHA document concerning treatment for fulminant myocarditis[70] calls for immediate administration of 1 g of solumedrol when an immune-mediated form of myocarditis is strongly suspected, before endomyocardial biopsy or other tests are performed. If the diagnosis of giant-cell myocarditis is confirmed, other immunosuppressive agents should be added.

Recently, empirical treatment with intravenous glucocorticoids in patients with cardiogenic shock or acute myocarditis complicated by heart failure, ventricular arrhythmias, or high-degree atrioventricular block has been proposed.[31] Maintenance therapy is then useful in patients with eosinophilic or giant-cell myocarditis, cardiac sarcoidosis, or a confirmed autoimmune disorder. In rare cases, a virus, such as enterovirus, cytomegalovirus, or adenovirus, is identified, and immunosuppressive therapy can be withdrawn.[80] In patients who are positive for PVB19 or HHV-6, maintenance of immunosuppression depends on the initial response to therapy and the viral load.[29,31]

Alternative condition-specific therapies for patients with virus-negative or autoimmune inflammatory cardiomyopathies include removal of autoantibodies (i.e., immunoadsorption) with subsequent intravenous immune globulin therapy,[81] and a large, multicenter study involving patients with dilated cardiomyopathy is ongoing. Intravenous immune globulin therapy is commonly used in pediatric patients,[82] but the use of such treatment in adults with lymphocytic myocarditis has been limited.

Data are insufficient to support antiviral therapy for acute myocarditis. The beneficial effects of interferon treatment on viral clearance and New York Heart Association functional class were shown only for adenovirus- and enterovirus-related, endomyocardial biopsy proven, chronic inflammatory cardiomyopathy.[83,84] Treatment with anti-herpesvirus drugs might be considered in patients with Epstein Barr virus, cytomegalovirus, or HHV-6 infection.[5] Whether a combination of antiviral and immunosuppressive therapy could be used in some patients with virus-positive inflammatory cardiomyopathy at some stage of the disease remains to be established.

Ongoing clinical trials are assessing the role of high-dose methylprednisolone in patients with acute myocarditis complicated by heart

failure or cardiogenic shock (the Myocarditis Therapy with Steroids [MYTHS] trial); of anakinra, an interleukin-1 receptor antagonist (Anakinra versus Placebo for the Treatment of Acute Myocarditis [ARAMIS]), excluding patients with a hemodynamically unstable condition; and of abatacept (a CTLA-4 directed fragment aimed at blocking T-cell costimulation by CD80 or CD86) for the treatment of immune checkpoint inhibitor induced myocarditis (Abatacept for the Treatment of Immune-Checkpoint Inhibitors Induced Myocarditis [ACHLYS]).[85]

## CONCLUSIONS

In the past 35 years, major progress has been made in our understanding of the regulation and diversity of cardiac inflammatory pathways implicated in the pathogenesis of myocarditis. The medical community looks forward to the development of standardized treatment regimens for patients with acute myocarditis.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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