Myocarditis is an inflammatory disease of the myocardium diagnosed using established histologic and immunohistochemical criteria (Table 1) (Figure 1). A recently published position statement by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases provides updated recommendations regarding the etiology, diagnosis, and therapeutic management of myocarditis. However, despite the formally structured definition, myocarditis is a heterogeneous disease, characterized by extensive variability in clinical presentation and ensuing evolution. This variability necessitates patient-tailored diagnostic and therapeutic management in which the advanced and often costly testing and treatments are reserved for those with the most severe and threatening clinical presentation. In fact, gaps persist between published recommendations and clinical practice, while real-world, applicable, hands-on guidelines for the practical management of the various manifestations of myocarditis are lacking.

Accordingly, this review summarizes the contemporary knowledge about myocarditis, offering a rational and practical approach for the management of this polymorphic disease. For this purpose, we searched the PubMed and MEDLINE databases for articles published from January 1, 1980, through December 31, 2015, using the following terms: myocarditis, inflammatory cardiomyopathy, and endomyocardial biopsy. Articles were selected for inclusion if they represented primary data or were review articles published in high-impact journals. In particular, a risk-oriented approach is proposed. The different patterns of presentation of myocarditis are classified as low-, intermediate-, and high-risk syndromes according to the most recent evidence on prognosis, clinical findings, and both invasive and noninvasive testing, and appropriate management strategies are proposed for each risk class.
substances, or physical agents. Once other specific causes are ruled out, most cases of myocarditis observed in clinical practice are attributable to viral infections and/or immune reactions. In particular, even when no viruses are detected by serologic and polymerase chain reaction (PCR) analyses, an unrecognized viral infection remains the most probable cause of idiopathic myocarditis. These cases are presumably observed in an advanced phase (usually 3 or 4 weeks after the infection) when the immune system has already achieved a complete clearance of the virus.

In consideration of the broad spectrum of clinical presentations, it is difficult to establish the actual epidemiological burden of myocarditis in the real world because its prevalence changes considerably in relationship to the population under study and to the adopted diagnostic criteria. For example, a recent epidemiological study identified myocarditis as the final diagnosis for 0.5% of all hospital admissions for cardiovascular reasons, frequently affecting a young population of mainly male patients. However, previous studies detected myocarditis on endomyocardial biopsy (EMB) in 10% to 17% of patients with otherwise unexplained cardiomyopathy. Similarly, myocarditis was found in 5% of individuals in a series of unselected and consecutive autopsies, but the disease was considered the main cause of death in only a minority. In this sense, it appears that myocarditis is underdiagnosed. Yet, it is obvious that the histopathologic characterization of this condition is not always necessary and gains practical relevance only in selected cases.
CLINICAL PRESENTATION AND DIAGNOSIS

The heterogeneity of clinical presentation of myocarditis ranges from subclinical, or benign, forms to major clinical syndromes, such as severe heart failure or life-threatening ventricular arrhythmias. In most cases, the clinical expression of myocarditis can be exemplified by 3 main patterns of presentation: (1) recent-onset heart failure (<6 months), (2) arrhythmias, and (3) chest pain. According to the position statement on the diagnosis and management of myocarditis from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, the clinical suspicion of myocarditis should arise in each of the aforementioned scenarios when the major contribution of other disease conditions, such as coronary heart disease, valvular heart disease, congenital heart disease, or hypertensive cardiomyopathy, has been excluded.

Of importance, the suspicion of myocarditis should take into consideration the mode of clinical presentation and some instrumental features at baseline and at short-term follow-up. These characteristics in fact could be useful tools in the prognostic stratification of patients with myocarditis in order to guide their further optimal management. As an implementation of current recommendations, this review proposes a practical and clinically oriented classification based on events risk.

Figure 2 illustrates the following 3 risk classes and the proposed clinical management:

1. High-risk major clinical syndromes. Prognosis largely depends on the short-term response to therapy and the evolution of clinical and functional parameters (eg, the presentation of recent-onset severe heart failure with severe left ventricular dysfunction and/or life-threatening arrhythmias).
2. Low-risk syndromes. These cases are typically characterized by a good long-term prognosis (eg, the presentation of chest pain and/or supraventricular arrhythmias with preserved left ventricular function and rapid [within 1-4 weeks] complete resolution of the electrocardiographic [ECG] and echocardiographic abnormalities).
3. Intermediate-risk syndromes. Although most cases of myocarditis are classified as high- or low-risk syndromes, some are characterized by the presence of structural or functional abnormalities, such as mild to moderate ventricular dysfunction, persistent wall motion or ECG abnormalities, late gadolinium enhancement in the absence of severe left ventricular dysfunction and remodeling on cardiac magnetic resonance imaging, or frequent nonsustained ventricular arrhythmias, that place them in a gray zone of prognostic uncertainty.

Typical findings for each risk scenario are provided in Supplemental Figures 1, 2, and 3 (available online at http://www.mayoclinicproceedings.org).

ROLE OF NONINVASIVE AND INVASIVE Diagnostic testing

The diagnostic work-up of myocardial inflammatory syndromes should be tailored to the severity of clinical/instrumental presentation and the short-term response to medical therapy (Figure 2).

Noninvasive Testing

Several noninvasive diagnostic tests with varying diagnostic potential and accuracy are available to clinicians for the diagnostic work-up of suspected myocarditis (Table 2). Personal

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**TABLE 1. Criteria for the Definition of Myocarditis**

| Histologic criteria: evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of nonischemic origin |
| Immunohistochemical criteria: abnormal inflammatory infiltrates defined as >14 leukocytes/mm² including up to 4 monocytes/mm² with the presence of >7 CD3-positive T lymphocytes/mm² |

**FIGURE 1.** Photomicrographs of active lymphocytic myocarditis (A, hematoxylin-eosin, original magnification ×20; B, immunohistochemical staining for HLA-DR antigen, original magnification ×20). Courtesy of Rossana Bussani, MD, Institute of Pathological Anatomy and Histology, Ospedali Riuniti and University of Trieste.
history, together with ECG, biomarkers, Holter monitoring, and echocardiographic features, should be thoroughly evaluated once other possible causes (ie, coronary artery disease, hypertensive heart disease, valve diseases) are excluded (Table 2). Once patients are classified into low-, intermediate-, or high-risk categories according to their clinical presentation, second-level examinations for the diagnosis of myocarditis should be undertaken.

In this sense, cardiac magnetic resonance imaging represents the criterion standard for the morphological/functional evaluation of cardiac structures and the characterization of the myocardial tissue, providing useful diagnostic and prognostic information in various clinical settings.10-12 However, cardiac magnetic resonance imaging has accessibility limitations and modest diagnostic accuracy in some clinical presentations, such as high- and intermediate-risk forms (Table 2).22 Furthermore, cardiac magnetic resonance imaging is poorly applicable in the presence of frequent ventricular and atrial arrhythmias.

FIGURE 2. Proposal for clinical management of patients with suspected myocarditis. ACEI = angiotensin-converting enzyme inhibitor; AV = atrioventricular; β-b = β-blocker; ECG = electrocardiographic; EMB = endomyocardial biopsy; HLA = HLA antigen; HTx = heart transplant; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVAD = LV assist device; LVEF = LV ejection fraction; MRB = mineralocorticoid receptor blocker; NYHA = New York Heart Association; PCR = polymerase chain reaction; PVB19 = parvovirus B19.
Endomyocardial Biopsy
Histopathologic analysis of myocardial tissue samples collected with EMB is the only way to definitively diagnose myocarditis. International recommendations about EMB implementation in clinical practice are controversial. The American College of Cardiology/American Heart Association guidelines recommend EMB in patients with severe clinical presentation in terms of recent heart failure or life-threatening arrhythmias. Conversely, the position statement on the diagnosis and management of myocarditis by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases expanded the spectrum of EMB indications, recommending this test for all cases of clinically suspected myocarditis regardless of the pattern and severity of clinical presentation.

In clinical practice, the value of EMB becomes crucial in detecting the specific histotype of the myocarditis and assessing the immunologic and virologic status of the myocardium through immunohistochemical and biomolecular PCR analyses. In this sense,

TABLE 2. Role and Typical Findings of Noninvasive Testing and Endomyocardial Biopsy in the Diagnostic Work-up of Myocarditis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history</td>
<td>Should always be thoroughly investigated&lt;sup&gt;4,10,11&lt;/sup&gt;</td>
<td>Flu-like symptoms, insect bite (for Borrelia or Rickettsia suspicion), timing of symptoms onset, family history of cardiomyopathy, drugs or toxic substances assumption</td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Troponin: typically elevated (no prognostic value)&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td>Troponin: low accuracy for detection of myocardial inflammation&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial serology</td>
<td></td>
<td>low accuracy for detection of myocardial infection&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Serologic analyses for autoimmune diseases</td>
<td></td>
<td>not to be routinely considered in the diagnostic work-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>may be useful to detect infections by Borrelia or Rickettsia in presence of clinical suspicion for bradyarrhythmias and advanced AV blocks</td>
<td></td>
</tr>
<tr>
<td>Serologic analyses for autoimmune diseases</td>
<td></td>
<td>Serologic analyses for autoimmune diseases should be considered only in the presence of clinical suspicion</td>
<td></td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Diffuse and saddle-shaped ST-segment elevation</td>
<td>Low voltages</td>
<td></td>
</tr>
<tr>
<td>Bravidarrhythmias or advanced AV conduction defects in the absence of LV dysfunction may be suggestive of infections by Borrelia or Rickettsia</td>
<td>Discordance between the severity of the clinical scenario and the scarcity of electrocardiographic alterations (absence of left atrial dilation and left intraventricular conduction delay)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Normal ventricular dimensions, morphologic features, wall motion, and global function</td>
<td>Global impairment of LV or biventricular function without major remodeling</td>
<td></td>
</tr>
<tr>
<td>Transient wall motion anomalies</td>
<td></td>
<td>Diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Transient mild ventricular dysfunction</td>
<td></td>
<td>Patchy alterations of the wall motion not responsive to coronary distribution or electrocardiographic alterations</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td></td>
<td>Pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Cardiac magnetic resonance imaging</td>
<td>Good accuracy&lt;sup&gt;11,18-20&lt;/sup&gt;</td>
<td>Modest accuracy&lt;sup&gt;14,21&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Distinction between myocarditis and acute coronary syndromes (subepicardial vs subendocardial/transmural LGE distribution)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>May be considered a conclusive diagnostic test</td>
<td>Modest accuracy&lt;sup&gt;14,21&lt;/sup&gt;, Cannot be considered a conclusive diagnostic test in the context of a major clinical syndrome</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography/computed tomography</td>
<td>In case of risk factors for coronary artery disease</td>
<td>In case of risk factors for coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>Not indicated</td>
<td>May be considered (case by case selection)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indicated in the presence of refractoriness to medical therapy in the short term</td>
<td></td>
</tr>
</tbody>
</table>

AV = atrioventricular; LGE = late gadolinium enhancement; LV = left ventricular.

<sup>1</sup> International recommendations about EMB implementation in clinical practice are controversial. The American College of Cardiology/American Heart Association guidelines recommend EMB in patients with severe clinical presentation in terms of recent heart failure or life-threatening arrhythmias. Conversely, the position statement on the diagnosis and management of myocarditis by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases expanded the spectrum of EMB indications, recommending this test for all cases of clinically suspected myocarditis regardless of the pattern and severity of clinical presentation.

<sup>2</sup> In clinical practice, the value of EMB becomes crucial in detecting the specific histotype of the myocarditis and assessing the immunologic and virologic status of the myocardium through immunohistochemical and biomolecular PCR analyses. In this sense,
EMB allows tailoring of therapy to the individual patient.25,26 However, EMB is invariably characterized by a mild, but not negligible, rate of major complications (around 1%) even when performed by experienced operators.27-29 Moreover, EMB has well-known limitations in its accuracy.30 Hence, EMB should be performed for the in-depth evaluation of recent-onset high-risk major clinical syndromes not responding to standard optimized medical therapy in the short term (from hours to 3 weeks after admission, on the basis of clinical status severity) (Table 3). In such cases, the definite EMB-driven diagnosis of myocarditis can offer additional information for clinical management: the in-depth characterization of the myocardial substrate can in fact provide the guide for a biopsy-driven therapeutic plan. Conversely, the value of EMB is questionable in patients presenting with low-risk syndromes and responding to standard care with no prospect of therapeutic or prognostic implication. Finally, in the setting of intermediate-risk syndromes, EMB should be considered on a case by case basis according to the clinical status of the patient and the presence of extensive structured myocardial involvement.

When EMB is performed, it is crucial to collect a sufficient number of tissue samples (⩾4).31 Although there are no clear recommendations, in our experience a biventricular approach is preferred,27,31 pending the procedural feasibility in the individual patient (eg, presence of left ventricular thrombosis or intra-aortic balloon pump). No clear evidence exists on the possible usefulness of cardiac magnetic resonance imaging in selecting the site of biopsy.27 Finally, it is crucial to ensure the appropriate preservation of the biopsy material and its subsequent evaluation in order to obtain the most exhaustive information from traditional histopathologic, immunohistochemical, and molecular virologic examination.32

NATURAL HISTORY AND PROGNOSTIC STRATIFICATION
Myocarditis is characterized by a highly variable natural history, ranging from quick resolution, to relapse, to the development of dilated cardiomyopathy and heart failure or unexpected sudden cardiac death.4 Thus, the identification of reliable early predictors of long-term prognosis is crucial for clinical management. A concise summary of the results of the main clinical trials and prospective studies reporting data on the outcome of myocarditis are reported in the Supplemental Table (available online at http://www.mayoclinicproceedings.org).

High-Risk Syndromes
It is well known that myocarditis is associated with severe and refractory heart failure generally characterized by poor prognosis, with a 60% heart transplant–free survival at 10-year follow-up.4,10 In particular, acute hemodynamic instability,33-35 intraventricular conduction abnormalities,36 and extensive structural derangement of the ventricular myocardium detected on late gadolinium enhancement at cardiac magnetic resonance imaging coexisting with left ventricular remodeling and dysfunction have emerged as early independent predictors of long-term prognosis.37 Nevertheless, an important variability exists among these patients regarding the further disease course, ranging from the complete recovery of ventricular function to progression to dilated cardiomyopathy. In fact, myocarditis represents a model of potentially reversible cardiomyopathy, and spontaneous or therapeutically induced improvement of ventricular function occurs within a few months after the onset of symptoms in 40% to 50% of patients initially presenting with left

<table>
<thead>
<tr>
<th>TABLE 3. Indications for Endomyocardial Biopsy</th>
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<tbody>
<tr>
<td>Severe congestive heart failure</td>
</tr>
<tr>
<td>Severe left ventricular dysfunction</td>
</tr>
<tr>
<td>Life-threatening ventricular arrhythmias</td>
</tr>
<tr>
<td>In the context of</td>
</tr>
<tr>
<td>Recent onset of the clinical syndrome</td>
</tr>
<tr>
<td>Refractoriness to conventional treatment in the short term (from hours to 3 wk after admission on the basis of clinical status severity)</td>
</tr>
<tr>
<td>Exclusion of other specific etiologies</td>
</tr>
<tr>
<td>Absence of severe left ventricular remodeling</td>
</tr>
<tr>
<td>Suspecting</td>
</tr>
<tr>
<td>Severe lymphocytic myocarditis</td>
</tr>
<tr>
<td>Giant cell myocarditis: major ventricular arrhythmias, atrioventricular blocks, autoimmune disorders, thyroma, drug hypersensitivity</td>
</tr>
<tr>
<td>Necrotizing eosinophilic myocarditis: ventricular thrombosis, hypereosinophilic syndromes, drug hypersensitivity</td>
</tr>
<tr>
<td>Cardiac sarcoidosis: major ventricular arrhythmias, atrioventricular blocks, extracardiac sarcoidosis</td>
</tr>
</tbody>
</table>

www.mayoclinicproceedings.org
ventricular systolic dysfunction.\textsuperscript{4,38} The improvement of left ventricular function in the short term (defined as an absolute increase of 20\% in the left ventricular ejection fraction or left ventricular ejection fraction >50\% 6 months after the first evaluation) has emerged as a predictor of favorable long-term prognosis, independent from baseline left ventricular function.\textsuperscript{4} Yet, the identification of clinically useful predictors of rapid improvement remains challenging.\textsuperscript{4} In this regard, magnetic resonance imaging is a promising tool because the absence of late gadolinium enhancement appears to be a strong predictor of left ventricular reverse remodeling in the setting of idiopathic dilated cardiomyopathy.\textsuperscript{39} Finally, a prospectively scheduled short-term follow-up increases the accuracy of long-term prognostic stratification of these patients because it is fundamental to assess the disease evolution in response to therapy (Table 4).

Few data are available regarding the prognosis for patients presenting with major arrhythmic instability. The available evidence indicates an intermediate risk of major events during long-term follow-up.\textsuperscript{4} In particular, patients presenting with marked signs of ventricular derangement, such as persistent ECG or wall motion abnormalities, severe ventricular functional impairment, or extensive burden on late gadolinium enhancement, seem to be at higher risk for recurrence of major arrhythmic events during midterm follow-up.\textsuperscript{40} However, because no reliable prognostic predictors have been identified for this subgroup of patients, a structured program of clinical and instrumental short-term reevaluation appears appropriate for the long-term management of these patients.

**Low-Risk Syndromes**

Patients presenting with chest pain, normal left ventricular function without wall motion abnormalities, stable arrhythmic profile, and complete resolution of ECG abnormalities in the short term can be considered definitively healed, with excellent long-term prognosis (Table 4).\textsuperscript{4,10,12,13}

The presence of troponin release is not prognostically relevant in the context of myocardial inflammatory syndromes and thus should not itself be a reason for a prolonged follow-up or additional investigation.\textsuperscript{13} Cardiac magnetic resonance imaging is an accurate tool in diagnostic work-up of this group of patients (Table 2). However, the presence of subepicardial late gadolinium enhancement, typically present in this condition, does not seem convincingly related to a worse prognosis when associated with preserved ventricular wall motion and a stable arrhythmic profile.\textsuperscript{13} Future studies in this peculiar setting are needed in order to confirm these findings. As mentioned previously, EMB does not appear to be indicated in the context of low-risk myocarditis.

**Intermediate-Risk Syndromes**

Despite the clear distinction between low-risk and high-risk syndromes, many patients still present with clinical, morphological, or functional features of prognostic uncertainty in which clinical decisions are not supported by the existing evidence. For instance, little

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of clinical reevaluations</td>
<td>1 mo, 6 mo, 2 y</td>
<td>3 mo, 6 mo, 12 mo, then yearly</td>
<td>3 wk, 3 mo, 6 mo, 12 mo, then yearly</td>
</tr>
<tr>
<td>Noninvasive testing</td>
<td>Assess ECG and echocardiographic normalization between 1 and 6 mo. Cardiac MRI is recommended</td>
<td>Periodic evaluation of LVEF and LV remodeling (ECG)</td>
<td>Periodic evaluation of the arrhythmic burden (Holter monitoring) Annual evaluation of arrhythmia induction during exercise test Cardiac MRI with LGE evaluation, if not assessed at disease presentation</td>
</tr>
<tr>
<td>Exercise restriction</td>
<td>Yes, for 2 y</td>
<td>Yes, lifetime</td>
<td>Yes, lifetime</td>
</tr>
<tr>
<td>Lifetime follow-up</td>
<td>No, if normalization at 2 y</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lifetime therapy</td>
<td>No, if normalization at 2 y</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ECG = electrocardiography; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = LV ejection fraction; MRI = magnetic resonance imaging.
evidence is available regarding patients presenting with chest pain and diffuse wall motion abnormalities, mild to moderate left ventricular dysfunction, or persistent ECG abnormalities. Data are also lacking for patients with frequent nonsustained ventricular arrhythmias and extensive late gadolinium enhancement in the absence of severe left ventricular dysfunction and remodeling. In these cases, prolonged clinical and instrumental follow-up is recommended because these findings may reflect the extensive myocardial derangement potentially leading to late arrhythmias or future evolution to left ventricular remodeling (Table 4). Notably, EMB may be helpful in the diagnostic work-up of this group of patients when findings on cardiac magnetic resonance imaging cannot be considered conclusive. In particular, EMB could be useful in diagnosing cardiac sarcoidosis or giant cell myocarditis allowing to plan an appropriate therapeutic management.7,27

**THERAPEUTIC ISSUES**

**Conventional and Supportive Therapy**

The therapeutic management of myocarditis should be based on the pattern and severity of the clinical presentation, the short-term response to conventional treatments, and spontaneous or therapeutically induced improvement. The main pattern of presentation, ie, heart failure, arrhythmias, and myopericardial inflammatory syndromes, should be treated with standard therapeutic regimens.

In the context of active myocarditis associated with severe left ventricular dysfunction, major clinical decisions, such as referral for heart transplant, left ventricular assist device, or prophylactic implantable cardioverter-defibrillator, should be deferred for 3 or 6 months, if feasible, and reevaluated according to short-term evolution under optimal medical treatment.4

Few data are available on myocarditis presenting with life-threatening or incessant ventricular tachyarrhythmias. In such cases, the indication for implantable cardioverter-defibrillator therapy is unclear and should be evaluated on an individual basis according to clinical presentation (eg, aborted sudden cardiac death or syncope), the magnitude of structural-functional ventricular derangement (eg, ventricular remodeling, presence of akinetic segments or aneurysmal deformation, extent of late gadolinium enhancement), the histopathologic substrate (eg, cardiac sarcoidosis or giant cell myocarditis), and therapeutic response to standard care.3,40 Likewise, referral for ablation should be considered in cases of persistent ventricular arrhythmias despite optimal medical therapy and identification of a structured substrate after excluding the inflammatory triggers.

**Immunomodulating Therapy**

Although numerous interventions targeting components of viral and immune responses (eg, immunosuppression,25,26,41 antiviral drugs,42 and intravenous immunoglobulin43) have been tested, none of them have been proved to impact survival. However, several small studies in well-selected patients found favorable effects in terms of ventricular function and clinical improvement,25,26 paving the way for ensuing well-designed, larger randomized controlled trials.

Immunosuppressive therapy with prednisone and azathioprine appears suitable for patients with EMB-proven active myocarditis with major clinical symptoms such as heart failure with severe ventricular dysfunction and/or life-threatening ventricular arrhythmias in whom conventional treatments have failed in the short term of 7 to 10 days. In this setting, the histopathologic diagnoses of giant cell myocarditis, necrotizing eosinophilic myocarditis, or cardiac sarcoidosis represent a clear indication for immunosuppressive therapy.30 Notably, current evidence suggests that in patients with lymphocytic myocarditis, immunosuppressive treatment should be administered only in the presence of increased tissue inflammatory markers25 and the absence of a viral genome,26 as identified on immunohistochemical and PCR analyses of myocardial samples.

Currently, the importance of a persisting viral genome in myocardial samples is strongly debated because of conflicting findings.10,33,42,44 In particular, controversies are focused on the role of parvovirus B19 that recently emerged as an endemic virus encountered with similar frequency in almost half of patients with perimyocarditis,45 dilated
cardiomyopathy,\textsuperscript{46} or other noninflammatory heart diseases.\textsuperscript{47-49} The full understanding of the role of parvovirus B19 and other viruses is crucial because currently, the presence of the viral genome in the myocardium detected by PCR represents a contraindication to immunosuppressive therapy for patients who would otherwise be clinical candidates. In such cases, a careful evaluation of the individual patient is mandatory. It is critical to cautiously consider the suitability of immunosuppression in cases with major clinical syndromes, refractoriness to maximal conventional therapy, and the absence of coronary vasculitis or viremia in blood samples.

Although there is a potential role for interferon treatment in the context of myocarditis with evidence of enteroviral infection,\textsuperscript{42} no randomized data are available regarding the effect of such therapy in all patients with myocarditis. Likewise, even though intravenous immunoglobulin treatment has been associated with significant improvement of ventricular function and viral load reduction in dilated cardiomyopathy\textsuperscript{44} and appears to prevent relapses in patients with recurrent pericarditis,\textsuperscript{50} it has not been validated in inflammatory myopericardial diseases.

Further studies are needed to better evaluate the role of specific antiviral and immunomodulatory treatments in patients with myocarditis and well-characterized virologic and immunologic profiles.

**CONCLUSIONS AND KEY POINTS**

Myocarditis is an underdiagnosed polymorphic disease with variable clinical presentation, evolution, and prognosis. The diagnostic approach and clinical management should be tailored to the clinical phenotype of the individual patient.

Patients presenting with chest pain and preserved left ventricular function typically have an excellent long-term prognosis and consequently should be managed conservatively. Once all ECG and echocardiographic abnormalities have disappeared during the short-term follow-up, such patients can be considered fully recovered. However, in the presence of extensive subepicardial late gadolinium enhancement despite the complete resolution of such abnormalities, a noninvasive follow-up prolonged up to 2 years is appropriate.

Patients presenting with severe left ventricular dysfunction and life-threatening arrhythmias represent a challenge in terms of diagnosis and clinical management, with some patients requiring advanced medical or mechanical hemodynamic support or even urgent referral for heart transplant. However, in consideration of the potential reversibility of the disease, a frequent reevaluation of clinical and instrumental parameters under optimal medical therapy is crucial for the appropriate management of these patients.

A careful clinical and instrumental evaluation guides the selection of patients at higher risk who could benefit from a comprehensive molecular evaluation of the myocardial substrate with EMB. The EMB-guided diagnostic work-up could guide the further tailoring of immune-interfering therapies. Despite emerging data supporting the use of such therapies in selected patient subsets, the evidence for the prognostic impact of immune-interfering or antiviral therapies is lacking and should be gathered in appropriately designed controlled trials.

**ACKNOWLEDGMENTS**

We thank Professor Raffale De Caterina, MD, PhD (Institute of Cardiology, G. d’Annunzio University, Chieti, Italy), for his support and motivation.

**SUPPLEMENTAL ONLINE MATERIAL**

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** ECG = electrocardiographic; EMB = endomyocardial biopsy; PCR = polymerase chain reaction

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REFERENCES


