JACC
VOL. 85, NO. 4, 2025

PUBLISHED BY ELSEVIER

EXPERT CONSENSUS DECISION PATHWAY

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

Endorsed by the Heart Failure Society of America, International Society of Cardiomyopathies, Myocarditis and Heart Failure, and the Myocarditis Foundation

Writing Committee

Mark H. Drazner, MD, MSc, FACC, *Chair*
Biykem Bozkurt, MD, PhD, FACC, *Vice Chair*
Leslie T. Cooper, MD, FACC, *Vice Chair*
Niti R. Aggarwal, MD, FACC
Cristina Basso, MD, PhD
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Jennifer E. Van Eyk, PhD

Solution Set Oversight Committee

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Gurusher S. Panjrath, MBBS, FACC
Barbara Wiggins, PharmD, FACC
Megan Coylewright, MD, MPH, FACC, *Ex Officio*

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in November 2024.

The American College of Cardiology requests that this document be cited as follows: Drazner MH, Bozkurt B, Copper LT, Aggarwal NR, Basso C, Bhave NM, Caforio ALP, Ferreira VM, Heidecker B, Kontorovich AR, Martín P, Roth GA, Van Eyk JE. 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. *JACC*. 2025;85:391-431.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2024.10.080

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TOP 10 KEY TAKEAWAY POINTS

1. Clinicians need to be aware of the 3 classic presentations of myocarditis: chest pain, heart failure (HF)/shock, and/or symptoms related to arrhythmia (eg, presyncope or syncope). In a young person, the history of an antecedent viral infection, or other risk factors that define stage A at-risk for myocarditis, followed by any of these cardiovascular symptoms should raise the suspicion of this diagnosis.
2. High-sensitivity cardiac troponin (hs-cTn) is a common diagnostic test in patients with suspected myocarditis; however, some patients with myocarditis will not have an elevated hs-cTn. Further research is needed to determine whether a normal level below the limits of detection of current fifth-generation assays can serve as an effective rule-out strategy for this diagnosis, and the prognostic utility of serial measurements.
3. Cardiac magnetic resonance (CMR) imaging and endomyocardial biopsy (EMB) are considered pivotal tests in the diagnosis of myocarditis. The former often allows the noninvasive diagnosis of stage B or symptomatic myocarditis. When CMR is performed, the diagnosis of myocarditis is based on detection of abnormalities in both T_1 and T_2 imaging; however, in patients with certain presentations—typically those with reduced ventricular function, deranged hemodynamics/symptomatic HF, or electrical instability—an EMB is warranted to diagnose specific conditions that require etiology-directed therapies, including immunosuppressive agents.
4. A novel 4-stage classification of myocarditis is proposed. Stage A refers to those having or exposed to risk factors; stage B to those asymptomatic but with evidence of myocardial inflammation; stage C to those with symptomatic myocarditis; and stage D to those with advanced myocarditis (hemodynamic or electrical instability requiring intervention).
5. Research is needed to define the trajectories of the 4 stages of myocarditis, including their risk of progression to chronic HF. Other key unanswered questions include the rate of progression from stage A to higher stages; how commonly stage B myocarditis occurs either during the development or resolution of myocarditis; what explains the variable rates of progression and improvement among patients; and when does stage D become irreversible?
6. Risk stratification in patients with symptomatic myocarditis guides the decision whether to refer to an advanced HF center with a multidisciplinary myocarditis team. There should be a low threshold to transfer patients with high-risk features, such as severely reduced ventricular function, symptomatic HF, hemodynamic instability, or electrical instability (either ventricular arrhythmias or heart block).
7. The follow-up of patients with myocarditis does not end after 2 to 3 weeks, even with resolution of symptoms. Two cardiac imaging studies are advised during follow-up. At an early interval after diagnosis (eg, 2-4 weeks), a repeat echocardiogram allows detection of new or progressive deterioration of left ventricular function suggestive of a diagnosis of giant cell myocarditis (GCM). A second follow-up imaging study, either a repeat echocardiogram (low-risk stage C myocarditis) or a CMR (if > low-risk stage C myocarditis or if stage D myocarditis), is advised at 6 months. Advocacy for insurance coverage of these tests is needed.
8. Given the increasing recognition of genetic predisposition to myocarditis, genetic counseling and testing is advised for all consenting patients. Discovery of a pathogenic variant should be followed by cascade screening of family members, thereby affording undiagnosed relatives the opportunity for clinical surveillance and, when appropriate, guideline-directed management and therapy.
9. Safety for return to strenuous physical activity is guided by a follow-up CMR, 24-hour monitoring for arrhythmia, and exercise testing, typically at 6

months after diagnosis. In some athletes, these assessments can be made as early as 3 months after the initial episode of myocarditis for consideration of return to competitive sports.

10. Further research on a wide range of factors is needed. These include how social determinants of health impact the development and progression of myocarditis; a need for international registries with diverse stakeholder involvement; improved phenotyping by novel biomarkers, imaging strategies, and refined pathological interpretation of EMB specimens, including the role of viral polymerase chain reaction (PCR) testing; the benefits of immunosuppression in lymphocytic myocarditis assessed in large prospective randomized clinical trials; whether unloading of the left ventricle for those on extracorporeal membrane oxygenation (ECMO) improves outcomes; and a greater understanding of the psychological burden on patients and caregivers following an episode of myocarditis.

1. INTRODUCTION

The definition, diagnostic strategies, prognosis, and recognition of etiologies for myocarditis have recently evolved. Currently, there is variability among classification and diagnostic criteria for myocarditis; an evolving role of imaging, biomarkers, and genetics in its diagnosis and risk assessment; and advances in treatment and management strategies for specific etiologies and severity of myocarditis. Thus, myocarditis was identified as a high-priority topic by the American College of Cardiology's (ACC's) Science and Quality Committee and the Solution Set Oversight Committee. Subsequently, the Writing Committee of the ACC Expert Consensus Decision Pathway (ECDP) on Strategies and Criteria for the Diagnosis and Management of Myocarditis was convened.

There is a growing recognition of the role of newer diagnostic modalities in the diagnosis and monitoring of myocarditis. This document provides new diagnostic criteria for myocarditis, taking such advances into consideration, as well proposing a new 4-stage classification of myocarditis.

Management of myocarditis varies according to severity of the presentation, stage of myocarditis, and specific etiology. It is important for specific etiologies to be identified to allow prompt initiation of appropriate treatment strategies and supportive care. This document addresses such treatment strategies.

Timely referral of severe myocarditis patients to specialists and medical centers with advanced diagnostic and management capabilities such as transplant and mechanical circulatory support is critically important. This document defines indications for referral to allow timely consideration of advanced therapies in high-risk patients.

Surveillance strategy, monitoring for recovery, and recommended activity restrictions vary according to the severity of presentation, specific etiology, comorbidities, and clinical trajectory. This document addresses indications for surveillance of recovery and guidance for return to activity. It is important to recognize that there is inadequate healthcare coverage for myocarditis care. For example, health insurance coverage may not include repeat imaging and/or testing following myocarditis diagnosis or initial testing with advanced imaging in the outpatient setting. This document emphasizes that patients may require repeat diagnostic evaluation to ascertain resolution of previously documented cardiac abnormalities, to define prognosis, and/or for consideration of additional therapies, such as guideline-directed management of cardiomyopathy or HF should they develop cardiac dysfunction.

Other topics addressed in this document include the role of genetic and social factors, knowledge gaps, and future research areas. This document is intended for clinicians taking care of patients with myocarditis, including cardiologists, HF clinicians, electrophysiologists, emergency room clinicians, radiologists, critical care specialists, and research scientists. Additionally, we believe it will be useful to alert payers, health networks, and administrators to the necessity of coverage for diagnostic strategies, including baseline and repeat imaging; laboratory, molecular, tissue, and/or genetic testing; and other advanced diagnostic testing.

In accordance with ACC's Relationship With Industry and Other Entities policy, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2. A list of abbreviations relevant to this ECDP can be found in Appendix 3.

For additional details concerning ECDPs please consult the Preface and Methods. To ensure full transparency, a comprehensive table of the writing committee's relationships with industry, including those not pertinent to this document, has been created. All of these items can be found in the online Supplemental Appendix.

2. ASSUMPTIONS AND PROPOSED DEFINITIONS

2.1. General Clinical Assumptions

1. The principal focus of this ECDP is on adults with acute myocarditis. For information on myocarditis in the pediatric population, the reader is referred to the "2021 AHA Scientific Statement on Diagnosis and Management of Myocarditis in Children."[1] This ECDP does not address conditions with chronic inflammatory

infiltrates of the myocardium, as this was considered beyond the scope of the paper.

2. The writing committee endorses the evidence-based approach to HF and cardiomyopathy diagnosis and management recommended in the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure"[2] and the "2023 ESC Guidelines for the Management of Cardiomyopathies"[3] and management of arrhythmia in the "2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death."[4]
3. Optimal care decisions should properly reflect the preferences of the managing clinician as well as the individual patient. In several circumstances, a shared-decision model regarding care decisions is appropriate, particularly when clinical equipoise exists in areas of treatment uncertainty.
4. This ECDP is not intended to supersede good clinical judgment as, especially for myocarditis care, many questions remain unanswered. Given the complexity of this condition, team-based care is optimal and, depending upon the severity of the presentation, may include a broad array of specialists.
5. This ECDP is based on the best clinical and scientific data currently available. As new discoveries emerge (eg, trials of additional agents, diagnostic strategies, and devices including other populations), these data will affect the recommendations made here. Clinicians should be careful to incorporate relevant information published after this ECDP.
6. Relevant portions of these recommendations are applicable to management in the ambulatory setting or the acute inpatient hospital setting.

2.2. Definitions

Acute myocarditis: An episode of clinically suspected myocarditis presenting within a short period of time (<1 month).

Guideline-directed management and therapy (GDMT): Treatment options supported for use by clinical practice guidelines.

HF: Defined as per the Universal Definition and Classification of Heart Failure,[5] symptoms and/or signs of HF caused by structural/functional cardiac abnormalities *and* at least 1 of the following: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion. An HF event, including hospitalization, is defined by the criteria outlined by the "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials."[6]

Advanced HF center: A center with multidisciplinary expertise that offers heart transplantation or implantation of durable left ventricular assist devices (LVADs).[7] Such centers have expertise to perform endomyocardial biopsies; provide circulatory support (eg, ECMO, LVAD, right ventricular [RV] assist device, and/or total artificial heart); and have a multidisciplinary cardiac and specialist team, including interventional cardiology, cardiothoracic surgery, HF, cardiac structural interventionalists, infectious diseases, clinical immunology, genetics counselors, and cardiac pathologists; provide advanced imaging including CMR; and provide genetic testing.

Multidisciplinary myocarditis team: An integrated team of health professionals with expertise in conditions relevant to the treatment of patients with myocarditis. Because patients with myocarditis may need urgent heart transplantation or implantation of LVADs, the myocarditis team typically would include all the expert members found at an advanced HF center. Additionally, the myocarditis team should be facile with advanced imaging modalities to assess myocarditis and myocardial tissue characterization, performance of EMB of native hearts in addition to transplanted hearts, ideally with the capability to perform voltage-gated EMB, and have ability to perform histopathological assessment of endomyocardial samples for myocarditis with immunohistochemistry (IHC) and viral PCR testing either within the center or by transfer of the biopsy specimens to a core laboratory via a defined and streamlined process.

HF with reduced ejection fraction (HFrEF): clinical diagnosis of HF and left ventricular ejection fraction (LVEF) ≤40%.[2,5]

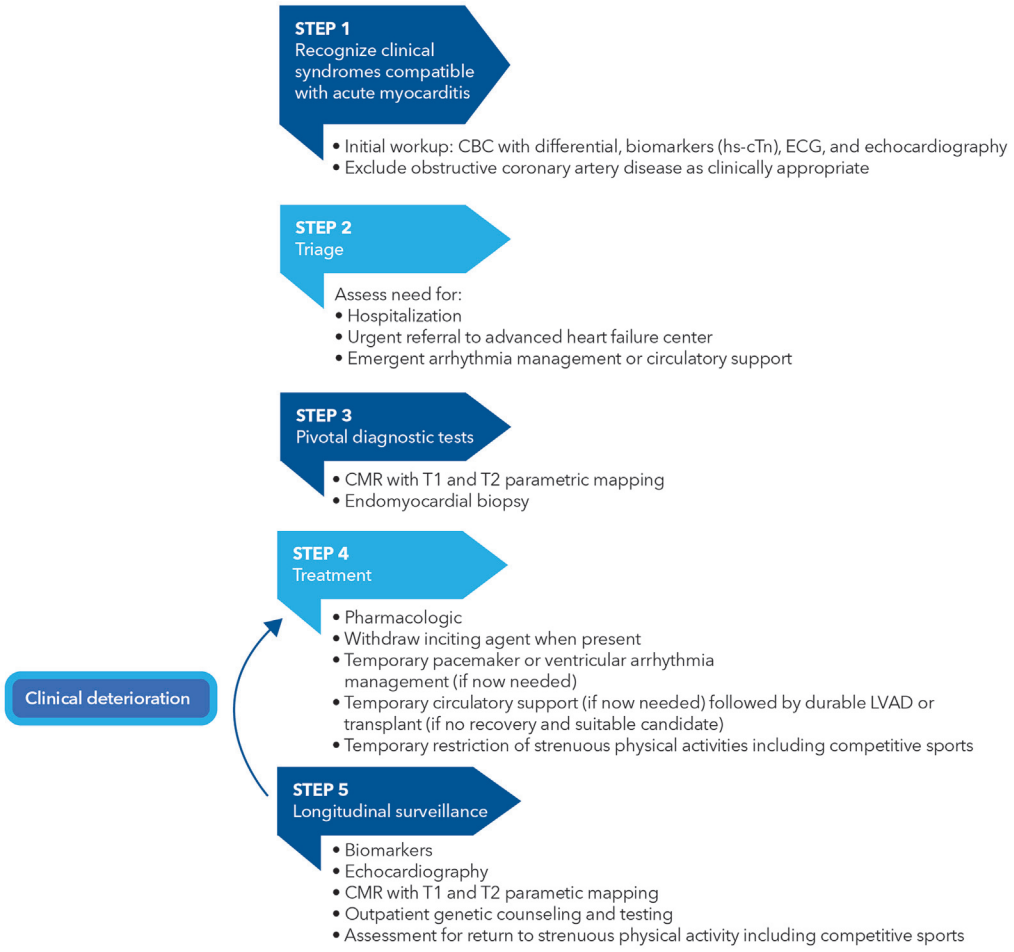
HF with mildly reduced ejection fraction (HFmrEF): clinical diagnosis of HF and LVEF 41% to 49%.[2,5]

HF with preserved ejection fraction (HFpEF): clinical diagnosis of HF and LVEF ≥50% not attributable to an underlying cause, such as an infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF.[2,5,8]

3. PATHWAY SUMMARY GRAPHIC

Figure 1 provides a summary graphic outlining the 5-step process for evaluation and management of clinically suspected myocarditis. The initial step is to recognize that a patient's clinical presentation might be consistent with the diagnosis of myocarditis. Given the numerous ways that myocarditis can manifest (**Figure 2** and Section 4.1.1), clinicians in a variety of healthcare settings need to be aware of this diagnosis. Examples include primary care physicians; rheumatologists; oncologists; substance abuse counselors or cardiologists in the ambulatory environment; personnel in the emergency department; hospitalists; intensivists; and cardiologists and subspecialty cardiologists (eg, HF cardiologists and electrophysiologists) in the inpatient setting. Once the diagnosis is considered, an initial set of screening tests, including an ECG, CBC with cell differential, circulating biomarkers

FIGURE 1 The Evaluation and Management of Clinically Suspected Myocarditis Described as a 5-Step Care Pathway



CBC = complete blood count; CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECDP = expert consensus decision pathway; ECG = electrocardiogram; hs-cTn = high-sensitivity cardiac troponin; LVAD = left ventricular assist device.

(hs-cTn, and in some cases, CRP and a natriuretic peptide level) and an echocardiogram should be obtained, if not already done. Obstructive coronary artery disease should be excluded by coronary angiography (invasive or via CT) as clinically appropriate. Triage decisions should be made at this initial evaluation based on the acuity of the patient's condition. Considerations include whether the patient needs to be hospitalized or referred to an advanced heart failure center with a multidisciplinary myocarditis team (Section 4.6.1), and whether emergent circulatory support or a pacemaker is needed for hemodynamic or electrical instability. Next, 2 pivotal tests to establish the diagnosis of myocarditis can be considered: a CMR, if the patient is stable for such, including T_1 and T_2 parametric mapping (Section 4.2.4), and, in select cases, an EMB (Section 4.2.6). Whereas myocarditis historically required a pathological diagnosis, advances in CMR and hs-cTn have permitted the noninvasive assessment of cardiac inflammation and/or injury. EMB can confirm specific types of myocarditis, including giant cell, eosinophilic, and sarcoidosis, as well as identify some infectious agents. Pharmacological treatment of myocarditis is initiated (Section 4.6.2) once the diagnosis is established, and, in some cases with clinical instability, when highly suspected. Further, if the patient's condition has deteriorated, the need for temporary circulatory support should be considered, if not previously implemented. A small minority of patients will not recover and require transition to a durable LVAD or heart transplantation. Patients in the outpatient setting should be educated to refrain from strenuous physical activity and competitive sports until cleared to return to such activities (Section 4.8). Required care does not end even if symptoms resolve after 2-3 weeks. Rather, patients need longitudinal

follow-up of myocarditis with repeat assessment of circulating biomarker levels, echocardiography, and usually a follow-up CMR (Section 4.7). A reassessment for return to strenuous physical activity, including competitive sports, can be performed at 3-6 months after initial diagnosis. Finally, outpatient genetic counseling and testing should be provided to consenting patients.

4. DESCRIPTION, RATIONALE, AND IMPLICATION OF PATHWAY

Based upon a comprehensive literature review and expert opinion, this ECDP aims to inform clinicians regarding the following: 1) the current diagnostic algorithm to follow in the setting of suspected myocarditis; 2) the pivotal role of advanced imaging and EMB in the confirmation of myocarditis; 3) when to refer patients to an advanced HF center and potential therapies for those with advanced myocarditis; 4) a new 4-stage classification of myocarditis, now including those "at-risk" for myocarditis and those with "asymptomatic myocarditis"; 5) recommendations for pharmacological treatment of myocarditis; 6) the need for longitudinal surveillance of patients with myocarditis, including a follow-up CMR; and 7) the growing importance of genetic predisposition for myocarditis. This document is intended for cardiologists of all subspecialties and frontline clinicians, including those in the emergency department and primary care settings.

4.1. Diagnosis of Myocarditis

4.1.1. Clinical Symptoms

The initial step for a clinician in the assessment of a patient with possible myocarditis is to recognize that a clinical scenario is consistent with this diagnosis. Although patients with myocarditis can be asymptomatic or have vague, nondescript symptoms, clinicians should be aware of 3 classic presentations as being consistent with this diagnosis: chest pain, arrhythmia, or HF/cardiogenic shock (**Figure 2**). The history of an antecedent viral infection (upper respiratory or gastrointestinal) in a young person, a prior diagnosis of myocarditis or autoimmune disease, a family history of cardiomyopathy or unexplained sudden death, or exposure to known cardiotoxin, followed by any symptoms potentially related to these 3 presentations should raise the suspicion for this condition.

4.2. Diagnostic Testing

Detailed below are some of the tests available to evaluate a patient with clinically suspected myocarditis. Two of these, specifically CMR with T_1 and T_2 parametric mapping and EMB with pathological analysis of the myocardial tissue, are considered pivotal in the diagnostic process. Because chest pain, electrocardiographic changes, and elevated high-sensitivity troponin (Tn) levels are common, many patients with suspected myocarditis will have undergone coronary angiography (invasive or via computed tomography) to exclude an acute coronary syndrome.

4.2.1. Electrocardiogram

Electrocardiogram (ECG) is widely used as an initial screening tool for diagnosis of myocarditis, despite its low sensitivity of 47%.[9] ECGs of patients with myocarditis often display a myriad of nonspecific findings, including sinus tachycardia, nonspecific ST/T-wave changes, low voltage, and PR-segment depression, none of which are pathognomonic for myocarditis.[10] A normal ECG or ECG with nonspecific changes do not rule out myocarditis but presence of pathological Q waves, left bundle branch block, wide complex QRS ≥120 ms, prolonged QT interval, high-grade atrioventricular (AV) block, malignant tachyarrhythmias, fragmented QRS, and T-wave inversion are often associated with decreased left ventricular function, presence of left ventricular scar and overall poor clinical prognosis in patients with myocarditis.[10-13] Involvement of the conduction system also raises the suspicion for sarcoidosis, GCM, or Lyme disease. Ongoing research, particularly by artificial intelligence, may improve our diagnostic capabilities and better risk-stratify patients with myocarditis.[14] ECG should be performed in cases of suspected myocarditis, but a normal ECG would not rule out presence of myocarditis.

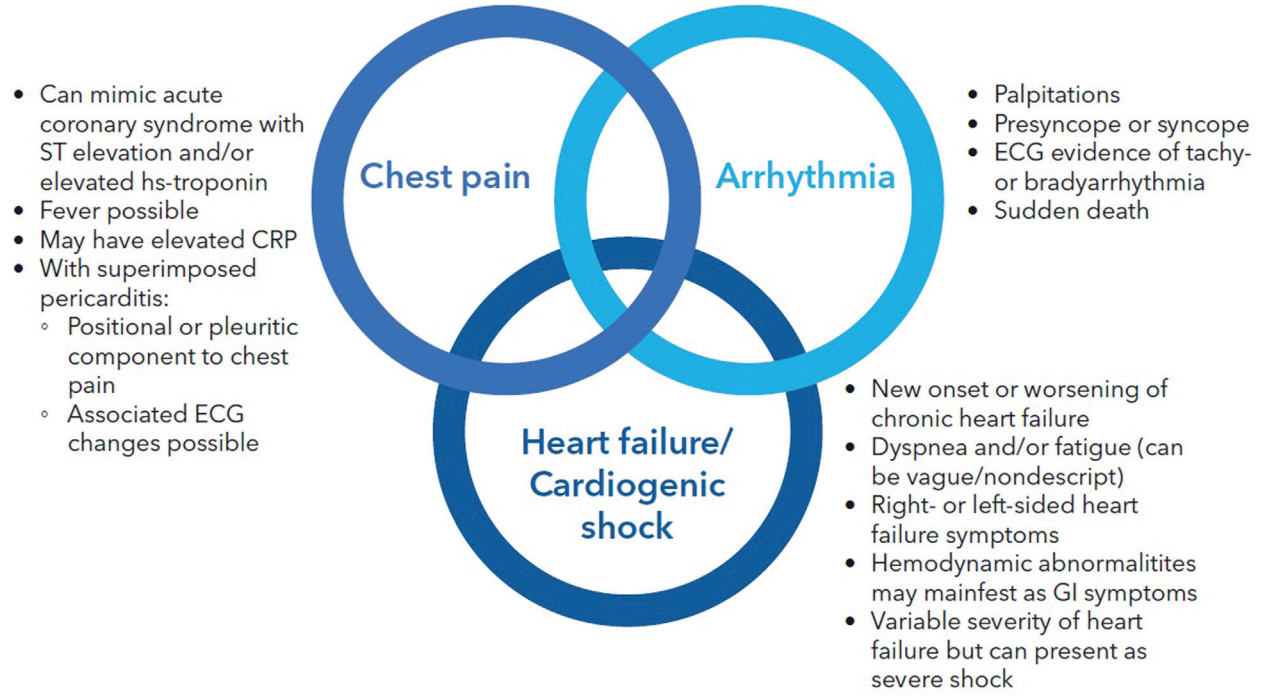
4.2.2. Echo and Strain Echocardiography

Transthoracic echocardiography is widely available and often serves as a screening tool to detect impaired left ventricular (LV) function in patients with suspected myocarditis[15]; however, its sensitivity is not adequate to rule out the diagnosis of myocarditis. LV dilatation, decreased LV function, increased wall thickness associated with myocardial edema, regional wall motion abnormalities, diastolic dysfunction, increased sphericity index, and signs of associated pericardial involvement can be seen in patients with myocarditis.[15,16] Fulminant myocarditis often presents with smaller cavity size and mildly increased wall thickness due to myocardial edema.[15] Abnormal myocardial mechanics, particularly LV global strain, may serve as a powerful diagnostic tool and add incremental value beyond ejection fraction.[12,17] LV longitudinal strain alterations and 2-dimensional echocardiographic features, however, are not specific for myocarditis and are commonly seen in other forms of HF.

4.2.3. Circulating Cardiac Troponin

Elevation of circulating cardiac troponin (cTn) in combination with other diagnostic tests can help with the diagnosis of myocarditis. Early studies demonstrated cTn

FIGURE 2 Three Classic Presentations of Myocarditis



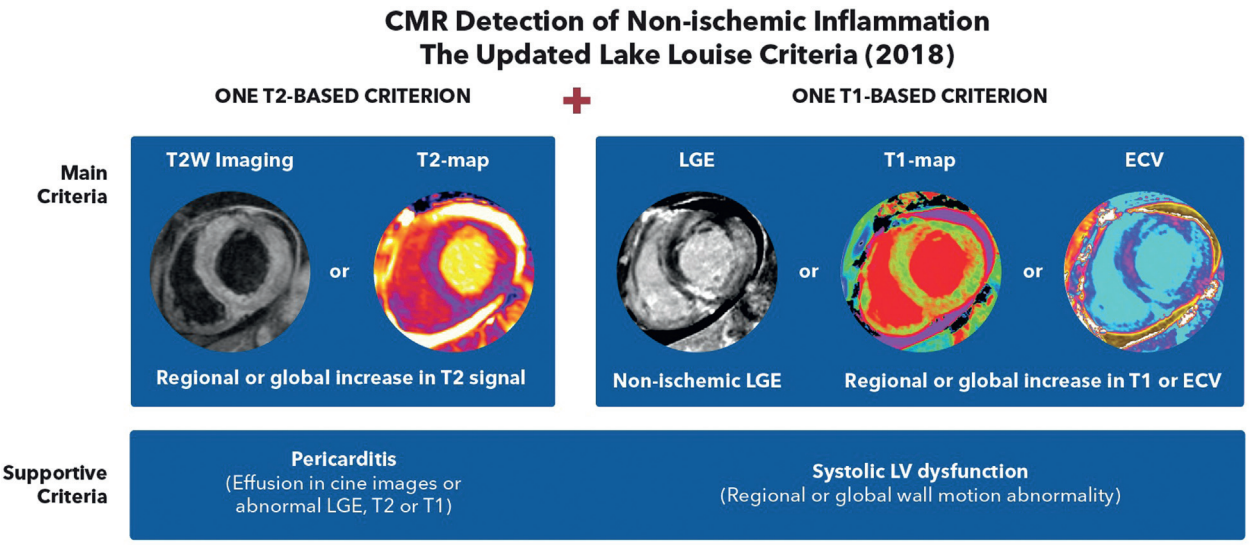
Patients can present with isolated or overlapping symptoms related to chest pain, arrhythmia, and/or heart failure/cardiogenic shock. CRP = C-reactive protein; ECG = electrocardiogram; GI = gastrointestinal.

had enhanced sensitivity compared with creatine kinase-MB to diagnose myocarditis.[18] Nevertheless, before modern high-sensitivity assays, elevated cTn only had a sensitivity of 34% to 71% and specificity of 86% to 94% for diagnosis of myocarditis.[19] Using less-sensitive assays, normal cTn values were reported even in those with fulminant[20] or GCM.[21] Cardiac enzymes can normalize despite ongoing disease activity and progression of late gadolinium enhancement (LGE) on CMR.[22]

The initial report of measurement of cTn via a high-sensitivity assay was in 70 patients with clinically suspected myocarditis and reported high-sensitivity TnT was associated with myocarditis with an area under the curve of 0.878.[18] The upper reference range corresponding with the 99th percentile of a normal population for the high-sensitivity TnT assay used in this study was 14 ng/L with a limit of detection of 5 ng/L. In acute myocardial infarction, single-value, rapid rule-out strategies often use lower threshold values at time zero near the limit of detection or limit of quantitation (eg, ~1-5 ng/L depending upon the assay used)[19] but to date, there are no published studies testing this strategy to exclude myocarditis.

There remain several challenges that impact interpretation of clinical hs-cTn immunoassays, especially at low elevation or borderline levels. First is the impact of sex (and age) on the circulating levels of cTn. Sex can influence the reference levels of hs-cTn[20-24] due to differences in heart size, hormonal state, structural differences in diseases and maladaptive processes (such as occurrence of macroscopic coronary plaque, development of fibrosis),[25,26] and presumably, the specific etiology and mechanisms (eg, viral vs immune checkpoint inhibitor [ICI] toxicity) driving the myocardial injury. Second, is whether the clinical immunoassays are impacted by either myocarditis-induced posttranslational modification of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) or whether there are autoantibodies against Tn protein present in the blood, both of which could negatively influence the clinically reported Tn values. As early as 2000, it was shown that cTnI and cTnT can be modified in human myocardium[27] and that the modified products could be found in the circulation.[28,29] Unfortunately, it remains unclear whether cTnI or cTnT are modified with myocarditis. Autoantibodies against cTnI[30] can induce myocarditis[31,32] in animal models[33] and in patients with dilated cardiomyopathy (DCM),[34] although the extent to which this may occur in patients with myocarditis remains unknown.

FIGURE 3 CMR Criteria for Nonischemic Myocardial Inflammation, as Seen in Myocarditis, Based on the Updated Lake Louise Criteria (2018)[42]



Parametric T1/T2/ECV maps provide pixel-by-pixel quantification of T1/T2/ECV values and are typically coded on a numerical color scale (scale not shown). Increased values on the T2 map are seen as orange/yellow, on the T1 map as red/purple, and on the ECV map as light blue within the LV myocardium. Pixel-wise numerical values may be obtained by using appropriate image post-processing software for advanced image analysis outputs. CMR = cardiac magnetic resonance; ECV = extracellular volume; LGE = late gadolinium enhancement; LV = left ventricular; T2W = T2 weighted.

4.2.4. Cardiac Magnetic Resonance Imaging

Myocarditis can lead to various pathophysiological changes in the myocardium that may be noninvasively detected using CMR. This modality is widely endorsed for assessing myocarditis in various statements and guidelines, the latter of which provide it a Class 1 indication.[35-47] CMR offers noninvasive multiparametric myocardial tissue characterization and is the gold-standard imaging test for assessing cardiac structure and function. Regardless of the etiology of myocarditis, the myocardial changes encountered can include myocardial edema (intracellular and interstitial); hyperemia, increased vascular permeability or capillary leak; myocyte injury and necrosis; and the formation of interstitial and/or focal fibrosis, and pericardial inflammation or effusion.

On CMR, the increased tissue water content in myocardial edema prolongs both T_1 and T_2 relaxation times[48] (**Figure 3**). T_1 and T_2 relaxation times are magnetic resonance properties of tissues, which are dependent on tissue type and surrounding milieu, biophysiological factors (such as sex, heart rate, and temperature), as well as technical factors (such as magnetic resonance hardware and software used to measure them). T_1 and T_2 relaxation times of tissues can be measured on a pixel-by-pixel basis in quantitative T_1 and T_2 maps. Each tissue type has a normal range of T_1 and T_2 values, the deviation from which may indicate disease states. Conventionally, myocardial edema is assessed by T_2-based techniques (such as T_2-weighted magnetic resonance imaging [MRI] and T_2 mapping), although T_1 mapping is also sensitive to detecting myocardial edema and inflammation. Hyperemia and capillary leak lead to a net expansion of the extracellular space, which can be detected using early gadolinium enhancement (EGE) imaging. Extracellular volume (ECV) is calculated via a formula that incorporates pregadolinium/postgadolinium contrast T_1 mapping values from the blood pool and the myocardium, and the hematocrit.[49]

Myocyte necrosis and focal fibrosis may be detected using LGE imaging. LGE lesions in myocarditis tend to be midwall and/or subepicardial, affecting predominantly the lateral and inferior walls, although subendocardial involvement can be encountered in combination with nonischemic patterns. Although LGE patterns are typically not pathognomonic for a specific etiology of myocardial inflammation, certain patterns or constellation of findings may suggest a potential diagnosis. For instance, diffuse subendocardial LGE beyond a single coronary territory associated with LV thrombus is often seen in eosinophilic myocarditis,[50] especially when multivessel obstructive coronary artery disease and a history of multiterritory myocardial infarctions have been ruled out. Striking ring-like midwall/subepicardial LGE patterns can be seen in desmoplakin[51] and other genetic

cardiomyopathies. Recognition of certain patterns of LGE may guide further diagnostic tests (including genetic testing) in search of the underlying etiology.

The updated Lake Louise Criteria (2018) for non-ischemic myocardial inflammation comprise at least 1 T_2-based criterion (global or regional increase of myocardial T_2 relaxation time or an increased signal intensity in T_2-weighted images) *in addition to* ≥1 T_1-based criterion (increased myocardial T_1, LGE, or ECV)[42,44] (**Figure 3**). Having only 1 (ie, T_2-based *or* T_1-based) marker may still support a diagnosis of acute myocardial inflammation in the appropriate clinical scenario, albeit with less specificity, suggesting that added caution is needed in such scenarios. Signs of pericarditis and ventricular systolic dysfunction serve as supportive criteria.

CMR strain imaging can detect subtler impairment in cardiac function and can be undertaken commonly using CMR myocardial tissue tagging, or feature-tracking of cine images. Strain parameters can be assessed in the longitudinal, circumferential, and radial directions. Layer-specific strain analysis, such as in the midmyocardial and subepicardial layers, where myocarditis lesions and injury tend to occur, may provide incremental diagnostic and prognostic value, even in LGE-negative areas.[52-55] LGE is a strong independent predictor of mortality in clinically suspected, CMR-proven myocarditis, with a hazard ratio 8.4 for all-cause mortality and 12.8 for cardiac mortality.[55] In contrast, diffuse LGE was not an independent adverse prognostic factor in 2 recent European studies of persons with biopsy-proven myocarditis.[56,57]

Overall, the updated Lake Louise Criteria have a high diagnostic performance and high sensitivity (>85%) for myocarditis.[42,58-61] Undoubtedly, this high accuracy depends upon the CMR being performed in centers with appropriate expertise in this imaging technique. The Updated Lake Louise Criteria allow the use of both quantitative mapping and conventional T_1/T_2-weighted CMR methods, although mapping techniques have demonstrated clinical utility in the detection of signs of myocarditis and advantages over conventional sequences.[58,60,62-66] Specialist centers implementing parametric mapping techniques should follow guidance from professional societal bodies, such as the Society for Cardiovascular Magnetic Resonance, which provide periodic expert consensus statements, guidelines, and also training in this area.[48] Per the Society for Cardiovascular Magnetic Resonance Mapping Consensus Statement from 2017,[48] CMR mapping sequences for clinical use should have a published clinical evidence base. Given that quantitative T_1 and T_2 relaxation times can vary by technical factors, such as magnetic resonance system hardware, magnet strength, and pulse sequence used, each center should establish local normal ranges, including sex-specific norms, to optimize diagnostic accuracy.[48,67] Phantom quality assurance solutions with clear pass-fail indicators for correct implementation at individual centers may be employed, before use for clinical use and trials.[68] Thresholds for abnormally high T_1 or T_2 values may be defined by convention as 2 standard deviations above the mean of the normal reference range, or established by dedicated validation studies in disease-specific patient cohorts. Methods for assessing the quality of parametric maps, such as T_1/T_2 curve-fits and quality-control maps (standard deviation, coefficient of determination [R^2], or residual maps), are important before using for clinical diagnosis.[48,69]

The ability of CMR to detect signs of myocarditis depends on the imaging techniques, protocol, and analysis, as well as the timing of imaging in relation to the myocardial injury. MRI-negative myocarditis may be encountered when MRI methods are not sufficiently sensitive or high resolution to detect the tissue changes, when there are limitations due to technical factors (such as tachyarrhythmia, motion, image artifacts) or insufficient coverage of the areas of interest (whole-heart vs selected slices in multiparametric tissue characterization), and when image analysis approaches fail to capture the areas of abnormality. The diagnostic yield of CMR in suspected myocarditis is typically highest when undertaken within the first 1 to 2 weeks of symptom onset, when the edema/inflammation are present to a degree that is detectable by current technologies. Data are lacking on the time evolution of acute edema and inflammation in acute myocarditis to address whether imaging too early from symptom onset may impact diagnostic yield. It is conceivable that acute myocyte necrosis may take time to develop from symptom-onset and may depend on the severity of the associated myocardial inflammation/edema; thus, using LGE alone to diagnose myocarditis on CMR may limit its diagnostic accuracy. Parametric mapping methods have higher diagnostic performance compared with conventional T_1/T_2-weighted methods (such as EGE and T_2-short tau inversion recovery) by circumventing some of the technical limitations, such as from breathing and cardiac motion, as well as by providing absolute quantification on a pixel-wise level without relying on reference regions of presumed normality for highlighting areas of pathology. CMR has lower sensitivity in patients with HF or arrhythmia in biopsy-proven myocarditis in some studies,[70] likely related to technical challenges due to patient difficulty in holding breath and irregular heart rhythms; technological advances, such as free-breathing and other MRI approaches that cope with tachyarrhythmias may continue to improve CMR's diagnostic performance in these patient groups.

Overall, CMR provides an attractive noninvasive diagnostic tool in evaluating patients with myocarditis. In

patients with cardiovascular risk factors, it may be reasonable to include stress perfusion into the CMR protocol in the appropriate clinical setting and, when safe to do so, to assess for signs of myocarditis and to rule out significant ischemic heart disease in a single examination. A CMR scan that has normal findings on edema imaging as well as on LGE and stress perfusion imaging can potentially avoid the need for further coronary imaging (such as coronary computed tomography [CT] angiogram or invasive coronary angiography), to rule out ischemic heart disease as a potential cause of the patient's presentation.

4.2.5. Other Imaging Tests

4.2.5.1. Nuclear Perfusion and Metabolic Imaging

Myocardial scintigraphy using inflammation-sensitive radiotracers may demonstrate focal patchy myocardial uptake in patients with myocarditis. Gallium scanning has a sensitivity of 36% and specificity of 98% for detection of biopsy-proven myocarditis in patients with DCM.[71] Furthermore, patients with viral myocarditis may also exhibit areas of decreased perfusion, detected by technetium-99m single-photon emission computed tomography (SPECT) imaging.[72]

Similar to SPECT imaging, focal ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake with positron emission tomography (PET) imaging is often seen in patients with myocarditis, reflecting metabolically active immune cells and presence of active myocardial inflammation.[73] ^{18}F-FDG PET allows imaging of myocardial inflammation due to increased uptake of ^{18}F-FDG in macrophage-dense regions of the myocardium. Macrophages are more metabolically active and more reliant on glucose as a metabolic substrate compared to normal myocytes.[74] Adequate preparation is essential to suppress physiologic myocardial ^{18}F-FDG uptake and improve assessment of myocardial inflammation on PET imaging. This may include prolonged (12-18 hours) fasting; 12 hours of a high-fat, low-carbohydrate diet; or intravenous heparin, often in combination.[74] The dietary manipulation facilitates switching of myocardial metabolism from glucose to fatty acid, and generally was found to be superior to prolonged fasting alone; however, optimal dosage and duration of this preparation is not well standardized across institutions.[74] Despite adequate dietary preparation, approximately 20% of patients may still experience nonspecific myocardial ^{18}F-FDG uptake.[75]

Despite these issues related to dietary preparation, ^{18}F-FDG PET has been shown to be beneficial in diagnosing myocarditis with arrhythmic presentation, with a specificity of 67% compared with that of EMB. Further, it may be a useful diagnostic strategy when CMR is not feasible due to arrhythmia or an implanted device that is not CMR compatible.[76] ^{18}F-FDG PET also offer incremental diagnostic capabilities to CMR by improving sensitivity for detection of myocarditis in cases of mild severity or longer duration than acute myocarditis.[77]

It is recommended to combine resting PET (ideally) or SPECT perfusion imaging with ^{18}F-FDG PET imaging to evaluate the full spectrum of myocardial inflammation. A normal PET examination demonstrates complete suppression of myocardial ^{18}F-FDG and normal resting myocardial perfusion. In contrast, patients with myocarditis typically have focal ^{18}F-FDG uptake with a corresponding perfusion defect. ^{18}F-FDG uptake without a resting perfusion defect may represent early inflammation without scarring. Caution should be exercised in the event of homogenous ^{18}F-FDG uptake typically due to failure to suppress physiologic myocardial ^{18}F-FDG uptake. Further, increased ^{18}F-FDG uptake is not specific to myocarditis and is seen in other states of myocardial inflammation, including myocardial ischemia.

4.2.5.2. Hybrid Imaging: PET/CT, PET/CMR

Hybrid PET/CMR imaging may offer incremental value vs either modality alone by simultaneously providing inflammatory, perfusion, and structural information.[78] A prospective, observational, multicenter cohort study to study the diagnostic and prognostic feasibility of ^{18}F-FDG PET/CT compared with that of CMR alone in patients with clinically suspected myocarditis (STREAM [Strategic Reperfusion Early After Myocardial Infarction] study) is ongoing; importantly, this study also includes correlation with EMB.[79]

4.2.6. EMB and Histopathological Analysis

EMB is recommended in clinical scenarios where the prognostic and diagnostic value of the information gained outweighs the procedural risks. Contemporary EMB Indications were updated in a 2021 position statement from the European, American, and Japanese heart failure societies.[80] The intent of the EMB is to achieve a diagnosis of certainty, thereby affording the opportunity for etiology-specific therapy (ie, antiviral or immunosuppressive/immunomodulatory) as well as excluding other disease entities that may mimic myocarditis.[80] In a propensity-matched, multicenter, retrospective cohort study, an EMB within 2 days of admission to the intensive care unit was associated with improved survival free of heart transplantation or LVAD implantation at 1 year.[81] Further details regarding indications for EMB are discussed in Section 4.4.6. The writing committee recognizes that many centers do not have the capability of performing an EMB or processing the biopsy samples, further underscoring the need to transfer patients who might need this procedure to an advanced HF team with multidisciplinary myocarditis capabilities.

EMB can suffer from sampling errors such that, when negative, it does not necessarily rule out the presence of

myocarditis; this is especially true when there are clear imaging signs of myocarditis in areas that may be difficult to access using EMB and when only the Dallas criteria are used.[82,83] Technical aspects to improve the diagnostic yield of the EMB include earlier timing after symptom onset (eg, within 2-4 weeks),[84] obtaining an adequate number (≥3) of samples, each 1 to 2 mm in size, and using voltage guidance to select myocardial sites for biopsy. The latter led to a sensitivity of 83% in a systematic review.[85] The myocardial tissue obtained should have samples immediately fixed in 10% buffered formalin at room temperature for light microscopy and other samples snap frozen in liquid nitrogen and stored at −80 °C or stored in RNAlater tubes at room temperature for viral PCR analysis. EMB sensitivity is higher when current immunological, immunohistochemical, and molecular tools are used, as will be described in the following text.[80,86,87]

There are risks of EMB.[80] The major complication rate (eg, death, cardiac perforation/tamponade, pneumothorax, thromboembolism, valvular trauma, severe arrhythmia) of EMB in experienced centers is generally <1%. The rate of minor complications (chest pain, deep vein thrombosis, puncture site hematoma or nerve palsy, hypotension/vasovagal syncope, arterial trauma, or vascular damage) has been reported between 5% and 6%. Procedural risk is increased in centers that infrequently perform EMB. The risks of EMB in children is generally higher than that of adults.

There is increasing sophistication in assessing the histopathological features of myocarditis in myocardial tissue, whether secured from EMB, as described in the previous text, or less commonly from surgical specimens or autopsy. The Dallas criteria, proposed in 1986, required the presence of inflammatory cells and myocyte necrosis/damage in the absence of ischemic characteristics associated with coronary artery disease. Two distinct diagnoses were then provided based on the initial and subsequent biopsies. The first EMB was assessed as showing (active) myocarditis, borderline myocarditis, or absent myocarditis; then by comparing the serial biopsies, a diagnosis of persistent (ongoing), healing (resolving), or healed (resolved) myocarditis was made. “Borderline” myocarditis was diagnosed when inflammatory infiltrates were present but there was no myocyte necrosis. The type of inflammatory cells present, eg, lymphocytic, polymorphous, eosinophilic, or giant cell, was identified via routine hematoxylin and eosin stain slides. This cell-type characterization afforded assignment of a specific etiology of myocarditis and conveyed prognostic information (**Figure 4**).

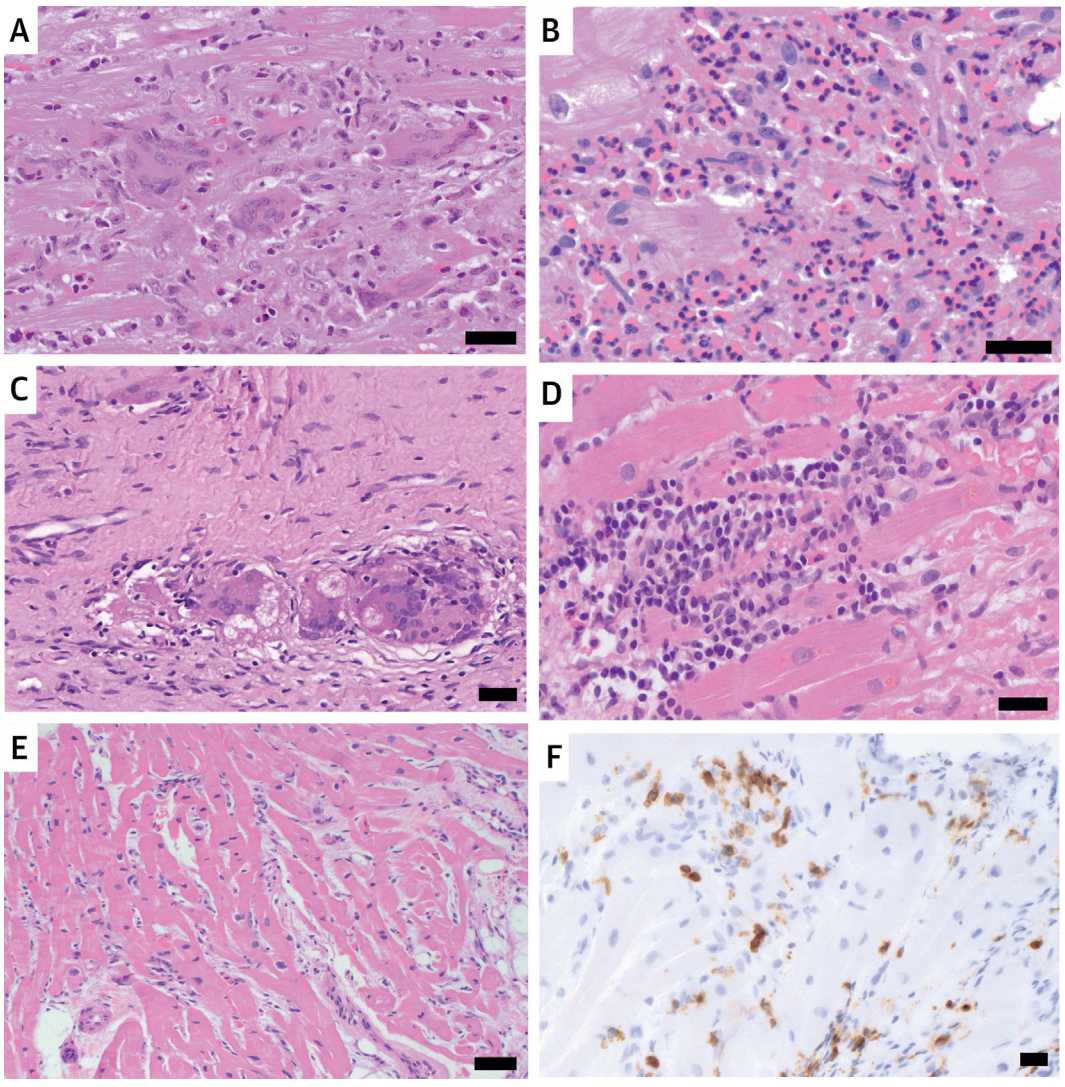
More recently, IHC has been utilized to assess for the presence of myocarditis. IHC is particularly helpful in the setting of focal or multifocal lymphocytic myocarditis, where the inflammation is not diffuse, by allowing detection of even small amounts of inflammatory cells/clusters and thereby increasing the sensitivity of EMB for this diagnosis. A large panel of monoclonal and polyclonal antibodies (including anti-cluster of differentiation [CD]3, T lymphocytes; anti-CD68, macrophages; and anti-HLA-DR [Human Leukocyte Antigen-DR isotype]) allows identification and characterization of the inflammatory infiltrate and the detection of HLA-DR up-regulation on EMB tissue sections as a marker of infectious-negative autoimmune myocarditis. Other immunofluorescence stains, such as C3d and C4d, as markers of immune activation, have been proposed but they require frozen material.

The World Health Organization/International Society and Federation of Cardiology criteria, based upon immunohistochemical count of inflammatory cells per high power field, eventually introduced a quantitative cutoff of ≥14 leukocytes/mm^2, including up to 4 monocytes/mm^2 with the presence of CD3-positive T lymphocytes ≥7 cells/mm^2. These criteria were adopted in the position statement by the European Society of Cardiology (ESC) for the diagnosis of myocarditis.[86]

In addition to IHC, molecular analysis with DNA-RNA extraction and RT-PCR amplification of viral genome enhances the utility of histopathological analysis of endomyocardial samples by assessing for systemic infection as the etiology of myocarditis. The writing committee is aware that many centers do not have familiarity or access to these techniques and that they are less commonly performed in the United States than in Europe. In addition to myocardial tissue, peripheral blood samples should also be tested by these methods. Quantification of virus load and determination of virus replication may add diagnostic value particularly when dealing with some viruses, such as parvovirus B19 and herpes simplex, but this also requires special tissue handling and cannot typically performed on samples that are formalin-fixed.

Unfortunately, there remains extensive variability in routine practice and criteria used to define, diagnose, and report myocarditis on EMB samples. In particular, the current practice suffers from 2 major limitations, ie, an extensive variability in the criteria used to define myocarditis, and the difficulty to achieve consensus particularly on “borderline” cases. Noteworthy, in a recent survey of the current practice on EMB, whereas 80% of responder pathologists said they employ the diagnostic criteria, only 40% use the ESC criteria and only 35% of pathologists use IHC in every suspected case of myocarditis.[88]

FIGURE 4 **EMB Diagnosis of Different Histotypes of Myocarditis**



(A) Giant cells; (B) eosinophilic; (C) sarcoidosis; (D) lymphocytic diffuse; (E) lymphocytic, focal; (F) lymphocytic, IHC diagnosis (CD3 positive interstitial cells). All may be diagnosed by routine H&E stain but in the setting of focal/mild myocarditis, IHC can be crucial in detecting inflammation. Scale bars (A, B, C, E: 20 μm; and D, F: 10 μm). EMB = endomyocardial biopsy; CD = cluster of differentiation; H&E = hematoxylin and eosin; IHC = immunohistochemistry.

4.3. Previous Diagnostic Criteria

4.3.1. World Health Organization

In 1995, the World Health Organization Task Force on Cardiomyopathies defined myocarditis as an inflammatory disease of the myocardium that is diagnosed by assessing an EMB specimen according to established histological, immunological, and immunohistochemical criteria.[83]

4.3.2. European Society of Cardiology

A position statement from the ESC Working Group on Myocardial and Pericardial Diseases in 2013[86] recommended that ≥1 of the following diagnostic criteria be met in addition to ≥1 of the above clinical presentations described previously (Section 4.1.1). If the patient is asymptomatic, ≥2 diagnostic criteria listed below should be met. Additionally, epicardial coronary artery disease

(stenosis ≥50%) or other known pre-existing cardiovascular (valve disease, congenital heart disease) or extracardiac (hyperthyroidism) causes that mimic the syndrome should not be present.

ESC diagnostic criteria for myocarditis from noninvasive testing included:

1. **Newly abnormal 12-lead ECG and/or Holter and/or stress testing**, any of the following: first- to third-degree atrioventricular block or bundle branch block, ST/T-wave change (ST elevation or non-ST elevation, T-wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R-wave height, intraventricular conduction delay, abnormal Q waves, low voltage, frequent premature beats, or supraventricular tachycardia.
2. **Elevation in circulating cTn** with a time course similar to that of acute myocardial infarction or a prolonged and sustained release (weeks or months).
3. **New, otherwise unexplained LV and/or RV structure and function abnormality on cardiac imaging (echocardiography/ventriculogram/CMR), including incidental finding in apparently asymptomatic patients:** regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilation, increased wall thickness, pericardial effusion, or endocavitary thrombi.
4. **New abnormal tissue characterization suggestive of inflammation by CMR:** structural myocardial changes suggestive of myocardial inflammation, such as myocardial edema, tissue changes, or fibrosis.

There are mimics of myocarditis to be aware of, including acute coronary syndrome, arrhythmogenic cardiomyopathy, idiopathic/genetic arrhythmias, noninflammatory nonischemic DCM/HF-infiltrative cardiomyopathies such as cardiac amyloidosis, or hemochromatosis. In presentations compatible with an acute coronary syndrome, CMR with tissue characterization criteria[42] is useful for differentiating myocarditis from ischemic injury.

4.3.3. Centers for Disease Control and Prevention and Brighton Collaboration

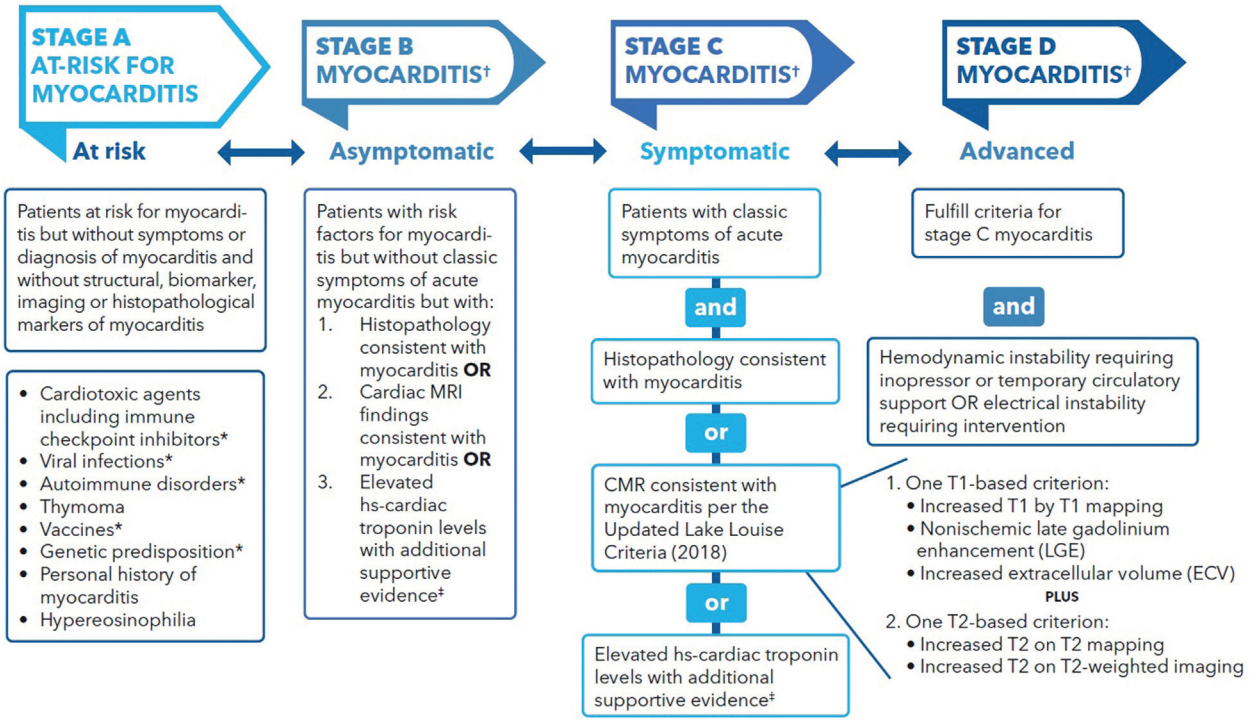
The Centers for Disease Control and Prevention published the vaccine safety surveillance case definition for myocarditis/pericarditis in 2003.[89] Precise adjudication criteria for classification as *suspected, probable, or confirmed acute myocarditis* or pericarditis were put forward. The diagnosis of confirmed acute myocarditis necessitated evidence of myocardial inflammatory infiltrate with necrosis/myocyte damage on histopathology assessment.

More recently, the Brighton Collaboration Myocarditis/Pericarditis Working Group proposed 3 levels of certainty for vaccine-related myocarditis.[90] The level of certainty 1 classification as a definitive case could be reached *either by* histopathological demonstration of myocardial inflammation *or* by a combination of elevated myocardial biomarkers with an abnormal imaging study (either CMR or echocardiography). If a patient had *compatible symptoms and 1 abnormal diagnostic test* (whether that be elevated cardiac biomarkers, ECG findings [eg, paroxysmal or sustained tachyarrhythmias, atrioventricular block grades 1-3, new bundle branch block], echocardiogram [wall motion abnormality, reduced LVEF, ventricular dilation, or change in wall thickness], or CMR in the absence of an alternative diagnosis for symptoms), then a probable case was assigned. Finally, the presence of *symptoms with either elevated circulating inflammatory markers* (C-reactive protein [CRP], erythrocyte sedimentation rate, D-dimer) *or less severe electrocardiographic changes* (eg, ST elevation, T-wave inversion, newly reduced R-wave height, abnormal Q waves, premature atrial and ventricular contractions) was classified as a possible myocarditis. A similar categorization of myocarditis in those being treated for cancer has been proposed.[91]

4.4. A New Classification of Myocarditis

A growing body of experimental and clinical evidence identifies some persons to be at risk of myocarditis yet without disease, and others who have evidence of subclinical cardiac injury and inflammation (ie, in the absence of the classic clinical symptoms described in the previous text). There also is a spectrum of severity of patients with symptomatic myocarditis that extends from those with minimal symptoms to those with severe manifestations, including hemodynamic compromise, the latter of whom need advanced therapeutic approaches. Finally, patients with myocarditis do not have static presentations but rather follow variable trajectories during longitudinal follow-up. The totality of these observations is similar to those seen in patients with symptomatic HF not related to myocarditis and are encapsulated in the 4-stage model of HF (stages A to D) with defined trajectories over time in the "2022 AHA/ACC/HFSA Guideline on the Management of Heart Failure."[2] Given these parallels between the 2 patient populations, the writing committee believed there would be value in applying a similar 4-stage approach to patients with myocarditis (**Figure 5**). We recognize that considerable work is needed to better define the natural history and therapeutic approaches for the 2 stages ("at-risk" and "asymptomatic") not typically described in patients with myocarditis. Nevertheless, this initial step of defining these stages should be an impetus for research in the coming years to fill these gaps in knowledge and thereby lead to advances in the field.

FIGURE 5 Proposed Stages of Myocarditis



The spectrum of myocarditis is described as 4 stages: A (at-risk); B (asymptomatic); C (symptomatic myocarditis); and D (advanced myocarditis). There are 2 pivotal tests to diagnose stages B-D myocarditis: EMB and CMR. EMB, including histopathology, immunohistochemistry, and molecular search for infectious agents, is the gold-standard diagnostic test for myocarditis, allowing characterization of histotype and specific etiologies (including viral). EMB is associated with some risks due to its invasive nature and limitations due to sampling error. CMR is an attractive noninvasive strategy although it too has limitations, including reduced sensitivity depending upon clinical presentation, a delayed timing after onset of symptoms, and technical challenges due to patient breath-holding and irregular heart rhythms. The specificity of CMR diagnosis of myocarditis is enhanced when both T_1 and T_2 criteria are met, although isolated T_1 or T_2 abnormalities may be seen at times. In the appropriate clinical context (eg, therapy with an immune checkpoint inhibitor), an acute rise in troponin can be consistent with the diagnosis of myocarditis but the specificity of an elevated troponin with most other stage A risk factors is not adequate to make the diagnosis and one of the two pivotal tests would be needed. Further, myocardial infarction needs to be excluded (eg, by coronary angiography or absence of ischemic LGE on CMR) as the basis of an elevated troponin level in most contexts when considering the diagnosis of myocarditis. Unlike the staging system in HFrEF, patients with myocarditis can move from higher to lower stages *Those known to be associated with myocarditis. †Pericarditis may complicate stages B-D ("myopericarditis"). ‡The level of supportive evidence depends upon the clinical context, including which stage A risk factor is present. CMR = cardiac magnetic resonance; EMB = endomyocardial biopsy; HFrEF = heart failure with reduced ejection fraction; hs = high sensitivity; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging.

4.4.1. Stage A

Risk factors to define stage A at-risk for myocarditis are shown in **Table 1**.

The risk of developing myocarditis varies with genetic background.[92] Recent studies in patients with myocarditis showed a significant fraction carry pathogenic genes variants linked with dilated and arrhythmogenic cardiomyopathy, suggesting that a gene-environment interaction may predispose to clinical myocarditis.[93,94] In contrast, whereas the major histocompatibility complex plays an important role in experimental models of immune-mediated/autoimmune myocarditis,[95-97] more data on human leukocyte antigens as well as other immune-response genes in biopsy-proven myocarditis are needed before patients harboring variants in these genes are classified in stage A. Given the emergence of the critical importance of genetic contributions to myocarditis, an in-depth discussion is provided in the following text (Section 4.4.1.1). Other persons at risk include those with a personal history of myocarditis; those treated with ICIs; those with thymoma, a tumor associated with myasthenia gravis; those with systemic immune-mediated diseases, such as sarcoidosis, lupus, rheumatoid arthritis, vasculitis, or hypereosinophilia; and those receiving or taking substances that convey cardiotoxicity (including adriamycin, trastuzumab, clozapine, cocaine,

TABLE 1 Risk Factors to Define Stage A At-Risk for Myocarditis

Genetic variants	■ Pathogenic gene variants linked to dilated and arrhythmogenic cardiomyopathy and neuromuscular disorders ■ Disease-causing variants in DSP and TTN are consistently associated with myocarditis
History of myocarditis	■ Personal history of prior episode of myocarditis ■ Family history of myocarditis
Cardiotoxins	■ Prescribed medications, including immune checkpoint inhibitors, doxorubicin, trastuzumab, clozapine ■ Illicit substances: cocaine, methamphetamine
Thymoma	
Systemic immune-mediated/ connective tissue disease	Sarcoidosis, systemic lupus, rheumatoid arthritis, scleroderma, myositis, or vasculitis
Hypereosinophilia	
Infectious agents	Particularly viruses (eg, adenovirus, enterovirus, parvovirus, human herpes virus 6, influenza, HIV, SARS-CoV-2) but also other organisms, including bacteria, fungi, and parasites
Vaccines	Including smallpox, mRNA COVID-19

COVID-19 = coronavirus disease of 2019; DSP = desmoplakin; mRNA = messenger RNA; TTN = titin.

or methamphetamine).[98] Numerous infectious agents, particularly viral,[99] and some vaccines,[100] also increase the risk of myocarditis. The clinical context and screening history and physical examination guide clinicians on sending diagnostic testing to detect such risk factors.

Although male sex is associated with a higher frequency of clinically suspected and biopsy-proven myocarditis, suggesting the role of testosterone in proinflammatory pathways, myocarditis in women with autoimmune features, in particular those with high titer antiheart autoantibodies and antinuclear autoantibodies, has a higher risk of death/heart transplantation.[101] Male sex was not listed as a risk factor defining stage A at-risk for myocarditis because the absolute risk of myocarditis among all men in the population remains low.

Symptom-free, healthy relatives of both familial and nonfamilial immune-mediated DCM who have antiheart autoantibodies are at increased risk of DCM development at 5 years, similar to other organ-specific autoimmune diseases like type 1 insulin-dependent diabetes mellitus.[102] Further work is needed to define whether patients harboring antiheart autoantibodies are also at increased risk of myocarditis.

The relationship between physical activity, sports, and myocarditis is complex. Vigorous exercise during infection can heighten the immune response and increase inflammation in the heart muscle due to immune suppression, cardiac stress, altered blood flow, and potential viral persistence.[103] A retrospective analysis of 82 physically active individuals revealed an association between high-static component sports and complicated myocarditis, whereas endurance activities were linked with uncomplicated disease.[104] Exercise-induced immunomodulation, particularly in endurance sports, might play a protective role, reducing myocardial inflammation and necrosis. Future studies are needed to assess these parameters as well as explore additional factors affecting myocarditis in athletes, such as psychological stress, travel, nutrition, and performance-enhancement medications. There is inadequate evidence to include physical inactivity or high levels of exercise as a risk factor for myocarditis.

4.4.1.1. Focus on Genetic Risk Factors

Host genetics have long been understood to determine myocarditis outcomes in animal models[105]; yet, only in the last decade have important human genetic factors been elucidated. Since the 1990s, myocarditis has been reported as a frequent histopathological finding in arrhythmogenic cardiomyopathy.[106] In 2015, myocarditis was described as the clinical presentation of arrhythmogenic cardiomyopathy, including in 5 individuals found to harbor predicted disease-causing variants in *DSP* or *LDB3*.[107] Shortly thereafter, rare, predicted causative variants in desmosomal genes (*PKP2*, *DSP,* or *DSC2*) were identified in 3 fatal cases of myocarditis suggesting that genetically mediated structural alterations impart myocardial vulnerability to pathogenic infection.[108] Additional case series have reported frequent (up to 92%) findings of pathogenic desmosomal gene variants in patients initially presenting with myocarditis[109] and later meeting task force criteria for arrhythmogenic RV cardiomyopathy.[110] More recently, there is an emerging concept termed “hot phases” of arrhythmogenic cardiomyopathy in which patients with at-risk genotypes present with findings consistent with stage B myocarditis on imaging and laboratory testing or a clinical syndrome of stage C or D myocarditis.[111] Further research is needed to understand whether such “hot phases” are clinically distinguishable from myocarditis as defined in this document.

The reports above formed the basis for formal genetic association studies in myocarditis. Although mice that lack genes encoding proteins related to immune pathways are more susceptible to myocardial coxsackievirus infection[112] and an adult patient with enteroviral myocarditis was reported to carry a rare, dominant-negative variant in a toll-like receptor gene (*TLR3*),[113] damaging variants in *TLR3*- or interferon-α/β-related genes were not enriched in 42 children with myocarditis on whole exome sequencing. Rather, rare biallelic variants in genes associated with cardiac structure and function were significantly enriched compared with that of healthy control subjects and individuals with other diseases, with 7 patients (16.7%) found to harbor homozygous or compound heterozygous nonsynonymous or splice-site gene

variations in *BAG3*, *DSP*, *PKP2*, *RYR2*, *SCN5A*, or *TNNI3*.[114] Several other case series subsequently reported results from targeted genetic testing (primarily cardiomyopathy gene panels) in small cohorts of patients with presumed or biopsy-confirmed myocarditis and identified likely pathogenic or pathogenic variants in 22% to 63% of cases, implicating additional genes (*DES*, *DSG2*, *DTNA*, *FLNC*, *LMNA*, *MYBPC3*, *MYH7*, *RBM20*, *TNNT2*, *TTN*).[115-119] In one such series, patients with myocarditis with relevant genotypes had significantly lower LVEF at follow-up (median: 71 months) than genotype-negative patients.[119] Interestingly, familial studies (cases and series) have repeatedly implicated *DSP* as a causal gene, including in cases of recurrent myocarditis or families with both myocarditis and DCM or sudden cardiac death.[109,120-122] In one series of 97 patients with myocarditis-confirmed by CMR or histology, patients with positive genetic testing (desmosomal gene variants) were more likely to have a family history of myocarditis, nonsustained ventricular tachycardia during the acute hospitalization, or specific LGE patterns (ring-like or septal) on CMR compared with those with negative genetic testing, suggesting that these features may be "red flags" for genetic forms of myocarditis.[120] More recent studies performing burden analyses for putatively damaging variants in patients with exclusively biopsy-confirmed myocarditis[123,124] or either biopsy- or CMR-confirmed myocarditis[125] have shown significant enrichment in relevant variation (8% to 17% genotype-positive) among established cardiomyopathy genes, as well as genes expressed in cardiomyocytes that are not as well established as predisposing to cardiomyopathy or are typically associated with neuromuscular disorders (*CTF1*, *DMD*, *DNM2*, *DYSF*, *PRDM16*, *RYR1*, *SGCG*, and *TRDN*) when compared with age-, sex-, and ancestry-matched control subjects; the most frequently implicated genes overall are *DSP* and *TTN*. Secondary analyses of these studies have drawn mixed conclusions, but no case-control studies to date have been sufficiently powered to meaningfully address the impact of harboring a relevant genetic variant on myocarditis outcome, or furthermore, any strong genotype-phenotype associations. The frequent clustering of both genetic susceptibility and environmental exposures within families complicates family-based studies.

Thus, persons harboring any of these pathogenic or likely pathogenic genetic variants should be classified as being at increased risk of myocarditis; however, it is important to recognize that the absolute risk of myocarditis conferred by harboring such variants is entirely unclear with no longitudinal studies of carriers. Given the relatively low incidence of myocarditis, such studies likely would require large quantities of carriers to be followed for many years to provide reliable estimates. Nevertheless, in a patient presenting with a syndrome that is potentially consistent with myocarditis, a family history of a nonischemic cardiomyopathy, or an event such as unexplained sudden death in a young relative, should heighten the suspicion for the diagnosis of myocarditis with a genetic predisposition in the presenting patient.

4.4.2. Stage B

In the proposed classification, stage B includes asymptomatic persons with CMR features of myocarditis or elevated hs-cTn, the latter in conjunction with additional supportive evidence of this diagnosis. The level of supportive evidence in the setting of an elevated hs-cTn in the absence of a CMR depends upon the clinical context, including which stage A risk factor is operative. For example, if receiving ICI therapy, an acute rise and markedly elevated Tn level in the absence of coronary artery disease may suffice for the diagnosis. In contrast, if the risk factor is a connective tissue disease, then additional features would be needed, such as echocardiographic findings compatible with the diagnosis. Finally, in some clinical presentations, a CMR would be required to distinguish stage B myocarditis from an alternative diagnosis, such as stress cardiomyopathy (eg, a patient hospitalized with influenza A, moderately elevated cTn levels, and reduced LVEF on echocardiogram).

Patients in stage B are by definition, asymptomatic, raising the question about how they will be identified. There are various scenarios in which this diagnosis can be made, including the following: 1) patients with stage C or D myocarditis who resolve their symptoms yet still have evidence of ongoing myocardial inflammation by circulating biomarkers or imaging modalities (ie, CMR) during longitudinal follow-up; 2) patients exposed to a cardiotoxin (eg, ICI therapy) who are surveilled for potential myocarditis, even if asymptomatic; 3) patients hospitalized with a viral illness who are found to have an elevated cTn or abnormal ECG upon admission, leading to further cardiac testing even without symptoms of myocarditis; 4) patients with other stage A risk factors, including systemic immune-mediated or connective tissue diseases, found to have an abnormal ECG on routine screening; and 5) patients undergoing cardiac screening for other indications (eg, perioperative testing or cascade screening) and found to have an abnormal ECG or arrhythmia on Holter monitoring, depressed ventricular function on echocardiography, or evidence of inflammation on CMR. It is not yet known how many patients with symptomatic myocarditis had a preceding asymptomatic phase, and, if so, for how long.

Evidence supporting the concept of stage B myocarditis includes the following. Murine models of myocarditis reveal that the first stages of inflammation are

characterized by down-regulation of homeostatic pathways and activation of resident cell immune responses in the heart.[126] These alterations in cellular activity and cytokine networks precede cardiac dysfunction and physical manifestations of HF. A prospective clinical investigation of smallpox vaccine demonstrated a rise in cTn can occur 10 days after vaccination without clinical evidence of myocarditis.[127] Prospective studies of COVID-19 infection in young athletes revealed approximately three-fourths of young athletes with CMR evidence of myocarditis were asymptomatic.[128] Persons treated with ICI frequently have elevations in cTn without symptoms.[129] Persons with symptomatic myocarditis can become asymptomatic over time yet continue to demonstrate evidence of inflammation on CMR; at that point, they would be classified as having stage B myocarditis.

Overall, further research is needed to understand the risks for the development and clinical significance of stage B myocarditis.

4.4.3. Stage C

Stage C refers to persons with symptomatic myocarditis. As described in the previous text, the manifestations vary widely and include chest pain, exercise intolerance, HF, and syncope from tachy- and bradyarrhythmias. For purposes of the proposed 4-stage classification of myocarditis, the diagnosis of stage C myocarditis requires several features to be present: 1) clinical symptoms typical of myocarditis (Section 4.1.1); 2) an absence of features that define stage D (advanced) myocarditis, detailed in the following text; and 3) CMR findings consistent with myocarditis based on *both* abnormal T_1 (T_1 mapping, LGE, or increased ECV) and T_2 parameters; *or* an elevated high-sensitivity Tn level (or less-sensitive Tn assay, as long as it is elevated) with supportive evidence; *or* an EMB consistent with myocarditis. As in stage B, the level of supportive evidence depends upon the clinical context, including which stage A risk factor is present. Patients with an initial presentation of a cardiomyopathy, as seen in those with symptomatic acute on chronic HF, may have an elevated Tn; in this context, either CMR or histopathological evidence would be needed to confirm the diagnosis of myocarditis.

Most patients with stage C recover from the acute illness but would remain as stage A patients since they are at-risk for recurrent myocarditis.[101] Occasionally, patients resolve symptoms but have evidence of ongoing inflammation on CMR or cardiac ^{18}F-FDG PET and/or elevated Tn. These patients would then shift to stage B. In this scenario, increased glucose metabolism on PET or prolonged T_1 and T_2 relaxation times on CMR may reflect a healing phase of inflammation characterized by regulatory macrophages and T lymphocytes.

4.4.4. Stage D

Stage D is defined as advanced myocarditis as evidenced by hemodynamic instability requiring inotropes/vasopressors or temporary circulatory support, or electrical instability requiring intervention. The latter would include high-grade AV block; frequent salvos of multifocal premature ventricular complex or nonsustained ventricular tachycardia; ventricular tachycardia; or ventricular fibrillation. Stage D myocarditis would include patients with Society for Cardiovascular Angiography and Interventions SHOCK stage C or higher.[130]

Prolonged and severe inflammation can lead to extensive and irreversible fibrosis with symptoms of advanced HF or refractory arrhythmias. Patients requiring mechanical circulatory or inotropic support are at highest risk with a 27% to 35% rate of death or heart transplantation in the 6 months following presentation[131]; however, even very severe cases with cardiac standstill can recover. The boundary between stage C and nonrecoverable stage D myocarditis is frequently uncertain. Additional clinical experience is needed regarding the value of immunosuppression for stage D myocarditis and how to determine when injury from myocarditis is beyond clinical recovery.

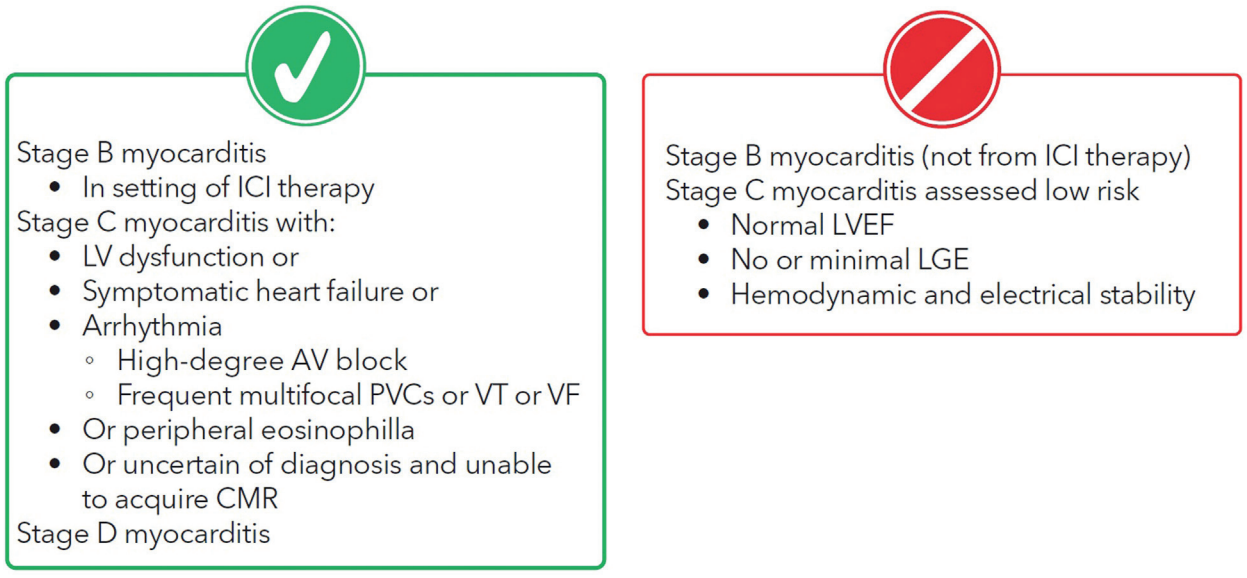
4.4.5. Myocarditis With Associated Pericarditis

In some patients, pericarditis is associated with myocarditis. Pericarditis may contribute to symptoms of chest pain and signs of pericardial rub on physical examination. On imaging studies, pericardial effusion may be noted, which is usually small or moderate in size, unless associated with systemic inflammatory disorders such as lupus, which may be associated with large pericardial effusions. Pericardial LGE may also be detected on CMR. There are inadequate data on the prognostic value of the coexistence of pericarditis with myocarditis compared with that of myocarditis alone. Myocarditis with associated pericarditis may reflect the extent of cardiac and systemic inflammation and imply causes beyond etiologies with cardiac myocyte tropism alone. Similar to that of viral myocarditis, viral myocarditis with associated pericarditis is usually self-limited and resolves without major complications or adverse outcomes. In the setting of systemic inflammatory disorders, myocarditis with associated pericarditis can be recurrent. In cardio-oncology, radiation therapy can result in pericardial inflammation in addition to myocardial injury.

4.4.6. Endomyocardial Biopsy

Indications for EMB, previously described in Section 4.2.6, can be overlayed on the new 4-stage classification of myocarditis (see **Figure 6**). Here, select stage B patients (ie, attributed to ICI therapy), more stage C patients

FIGURE 6 When to Perform EMB in Patients With Suspected Myocarditis



AV = atrioventricular; CMR = cardiac magnetic resonance; EMB = endomyocardial biopsy; ICI = immune checkpoint inhibitor; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

(ie, LV dysfunction, HF, arrhythmia, peripheral eosinophilia, or unable to acquire CMR with uncertain diagnosis), and most stage D patients should undergo biopsy.

4.5. Prognosis and Trajectories of Myocarditis

4.5.1. Prognosis

Biopsy-proven acute/active myocarditis resolves in about 50% of cases in the first 2 to 4 weeks, but approximately 25% will develop persistent cardiac dysfunction, and 12% to 25% may deteriorate and either die or progress to end-stage DCM/heart transplantation. Short- and long-term natural history of myocarditis varies as a function of etiopathogenesis, clinical presentation, and disease stage at EMB (acute/active, chronic, fibrosis).

Risk stratification on index presentation is vital for management (Table 2).

Biventricular dysfunction is the main independent predictor of death or transplantation. Univariate negative predictors include HF presentation, advanced NYHA functional class, and cardiogenic shock. It is still unclear whether an arrhythmic presentation is an independent adverse risk factor, but recurrent ventricular tachyarrhythmias or advanced-degree AV block portends poor prognosis. In a single-center prospective study of 96 adult patients with clinically suspected myocarditis with arrhythmia presentation of any type, who underwent EMB and programmed ventricular stimulation, independent risk factors for malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, or appropriate implantable cardioverter-defibrillator discharge) at follow-up included arrhythmic onset by sustained ventricular tachycardia or ventricular fibrillation, fibrosis at EMB, and positive programmed ventricular stimulation.[132] The presence of LGE on CMR is another powerful prognostic factor for adverse outcome, especially in an anteroseptal location but further data are needed to determine whether the overall extent of LGE provides additional prognostic information.[56,57,62,133]

Baseline Tn by itself is typically not considered a negative predictor, possibly because many patients with a presentation compatible with an acute coronary syndrome have preserved biventricular function; however, hs-cTnT values within 72 hours of diagnosis, specifically in the setting of ICI myocarditis, did provide important prognostic information.[134] Additionally, in patients with fulminant myocarditis, a decrease in hs-cTnI over 24 and 48 hours was associated with reduced in-hospital mortality,[22] suggesting serial measurements of high-sensitivity Tn assays can provide prognostic information. Further studies on this strategy are needed.

If all histological types, ie, eosinophilic and GCM, are included in survival analysis, fulminant presentation is a

TABLE 2 Key Risk Factors for Adverse Prognosis in Patients With Myocarditis

Clinical Presentation	Echocardiography	CMR	Histology
Symptomatic HF	Biventricular reduced EF	Biventricular reduced EF	GCM
Cardiogenic shock		Presence of LGE	
Electrical instability ■ Recurrent ventricular arrhythmia ■ Advanced AV block			

AV = atrioventricular; CMR = cardiac magnetic resonance; EF = ejection fraction; GCM = giant cell myocarditis; HF = heart failure; LGE = late gadolinium enhancement.

risk factor for adverse outcome. Most studies suggest that survival rates are worse in GCM, a rare autoimmune form,[135] associated with refractory HF and life-threatening arrhythmia. A study, before the introduction of immunosuppression, has shown that young age and a previous episode of myocarditis were independent predictors of relapses; autoimmune features, in particular women, high-titer serum antiheart autoantibodies, and antinuclear autoantibodies, were independent predictors of death and heart transplantation.[101]

Contrary to the common perception of good long-term prognosis in patients with acute myocarditis, there is an overall increased risk of mortality, life-threatening ventricular arrhythmias, HF, and disease recurrence rate of 11.5% over a mean follow-up of 2 years.[133] In particular, the presence of LGE and LGE in the anteroseptal location heralded a 3- and 2-fold increased risk, respectively, of mortality and major adverse cardiac events during a mean 2-year follow-up. In another study, LGE was the strongest independent predictor of mortality in myocarditis among clinical and imaging parameters (all-cause mortality hazard ratio [HR]: 8.4; cardiac mortality HR: 12.8).[136] In contrast, diffuse LGE was not an independent adverse prognostic marker in 2 recent studies.[56,57] Reduced LVEF is another important adverse prognostic marker in myocarditis.

4.5.2. Trajectories of Myocarditis

There remains much to be learned about the trajectories of those individuals with stage A and B myocarditis (see Figure 7). For stage A, the absolute risk conveyed by many risk factors is unknown, as is why some patients will progress from stage A to stage B, C, or D myocarditis. Aside from removal of offending agents (eg, a chemotherapeutic agent or illicit substance like cocaine), it is not known what therapies can be instituted to prevent the progression to higher stages of myocarditis. It also is not known why some patients rapidly progress from risk factor to fulminant myocarditis, whereas others do so over longer periods of time. Likewise, it is unknown how common stage B myocarditis is in the transition from stage A to stage C or D myocarditis. It also is not known how often stage B myocarditis progresses to higher stages and over what time interval. Further, additional research is needed to define the short-, intermediate-, and long-term risks of clinical HF and rhythm disturbances in those with stage B myocarditis.

In stage C myocarditis, the risk of recurrence varies from 3% to approximately 10% per year and may be influenced by the presence of desmosomal gene variants.[101,120] Remission, defined as symptomatic and ventricular functional improvement, is common in HF patients with myocarditis treated with GDMT. After clinical and functional recovery in acute nonischemic DCM, the risk of recurrent heart failure after standardized withdrawal of GDMT is substantial.[137] Defining the risks of short-term major adverse cardiac events after similar medication withdrawal in patients with myocarditis and of delayed ventricular stiffening leading to HFpEF[138] will require long-term studies in diverse cohorts with specific causes of myocarditis.

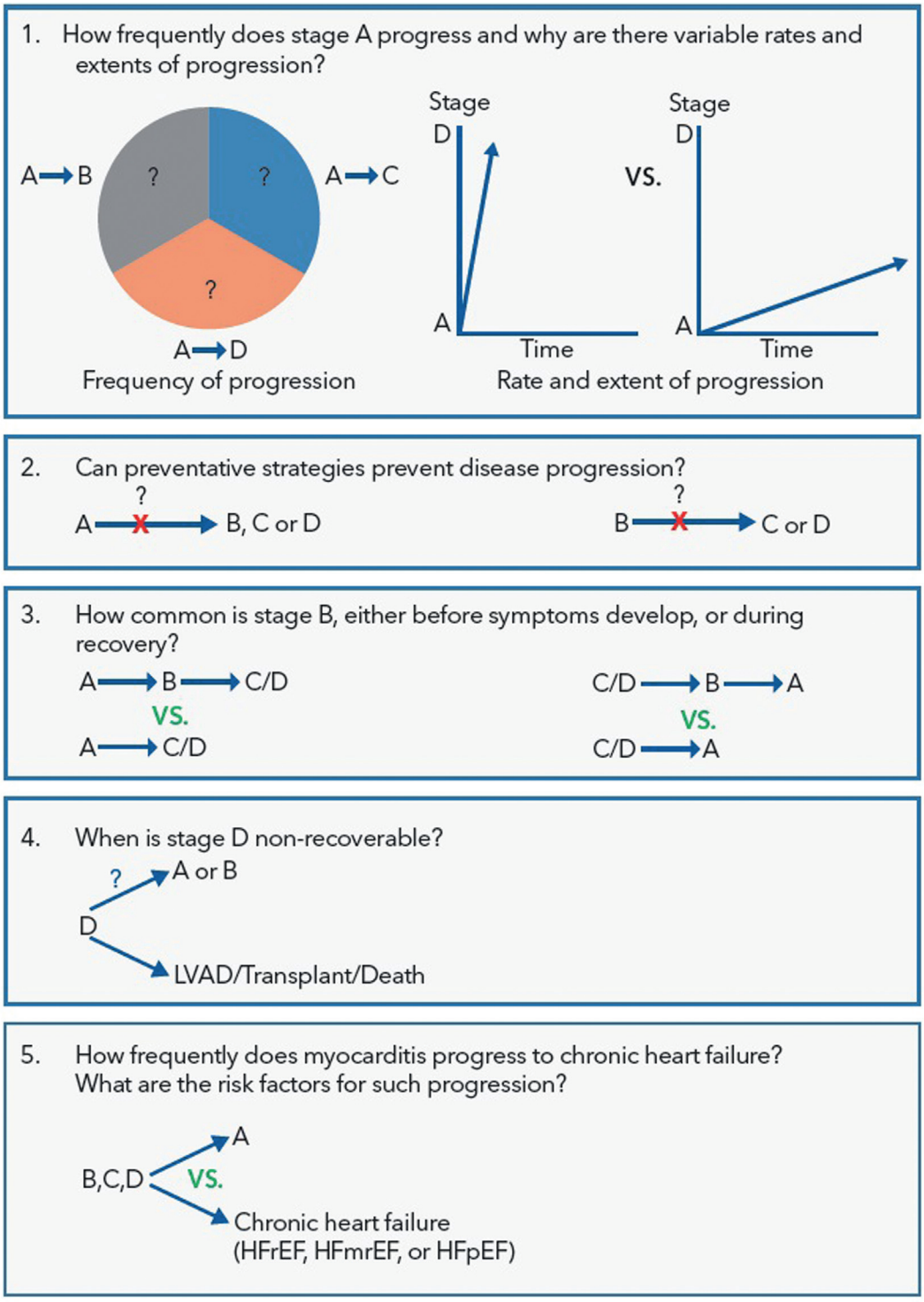
The trajectory of stage D myocarditis can be variable. Patients can progress to cardiac standstill but also can fully recover their ventricular function. Whereas previous studies suggested those with fulminant myocarditis (comparable with stage D) often recovered more dramatically than those with a nonfulminant presentation, more recent data caution that may not be the case. In an Italian study of 187 patients with acute myocarditis, of which 55 were characterized as fulminant, the rate of in-hospital death or transplantation was 25.5% in the advanced myocarditis group vs 0% in those with less severe presentations.[139] Additionally, after a median follow-up of 22 months, 29% of patients with fulminant myocarditis still had an LVEF <55%.

Overall, further research is needed to determine how frequently stages B, C, and D myocarditis progress to HF and its subtypes of HFrEF, HFmrEF, or HFpEF.

4.6. Treatment of Myocarditis

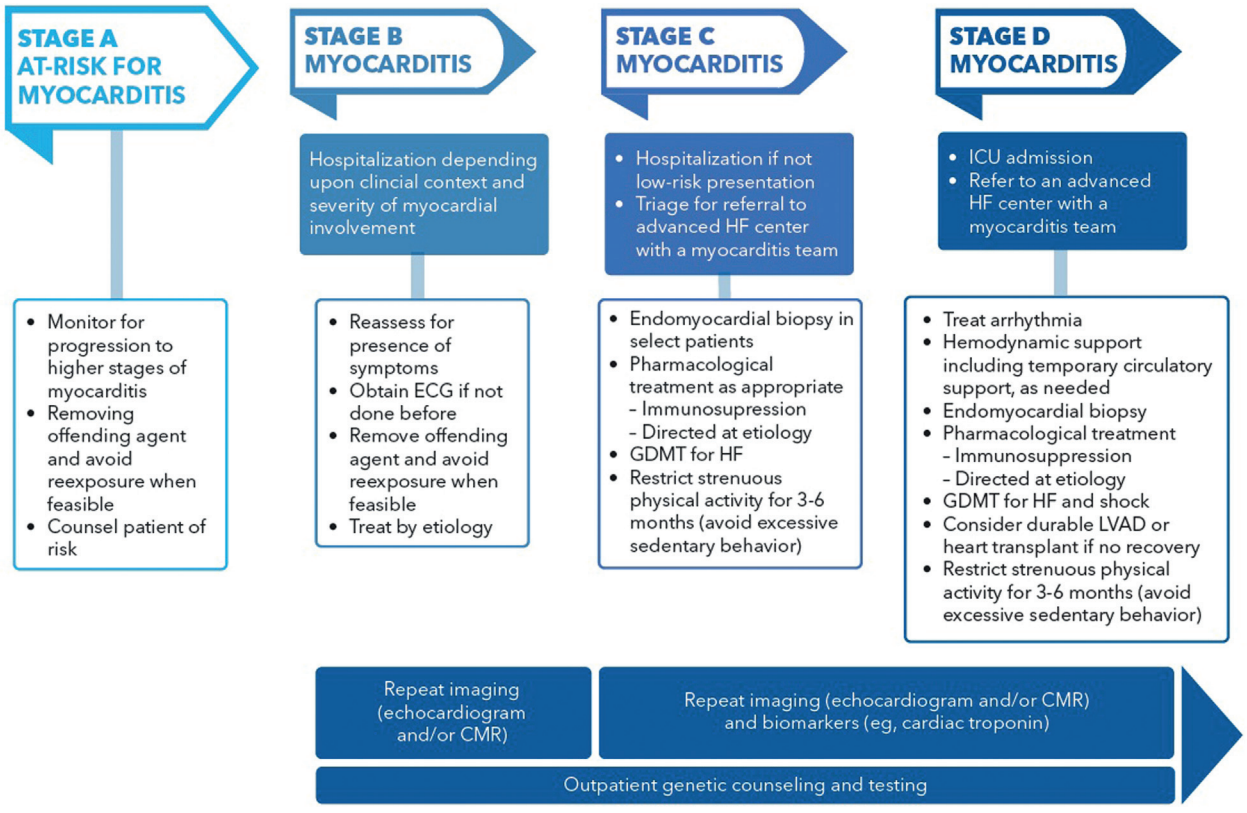
An overall management algorithm of the 4 stages of myocarditis is shown (see Figure 8). Those in stage A should be monitored for onset of symptoms, have the inciting agent removed (eg, cocaine or methamphetamine, or in those with a prior history of myocarditis, consideration of discontinuation of pharmacological therapies known to cause myocarditis, when feasible), and counseled about the risk and symptoms of myocarditis. Those in stage B should have all the above done but also should have a reassessment by their clinician for presence of symptoms; an ECG and hs-cTn (if not done previously); and in selected biopsy-proven cases, consideration of immunosuppressive therapy (eg, patients receiving ICI therapy). The need to hospitalize a person with stage B myocarditis depends upon the clinical

FIGURE 7 Key Unanswered Questions Regarding Trajectories Across Stages of Myocarditis



LVAD = left ventricular assist device; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

FIGURE 8 Surveillance and Treatment by Stage of Myocarditis



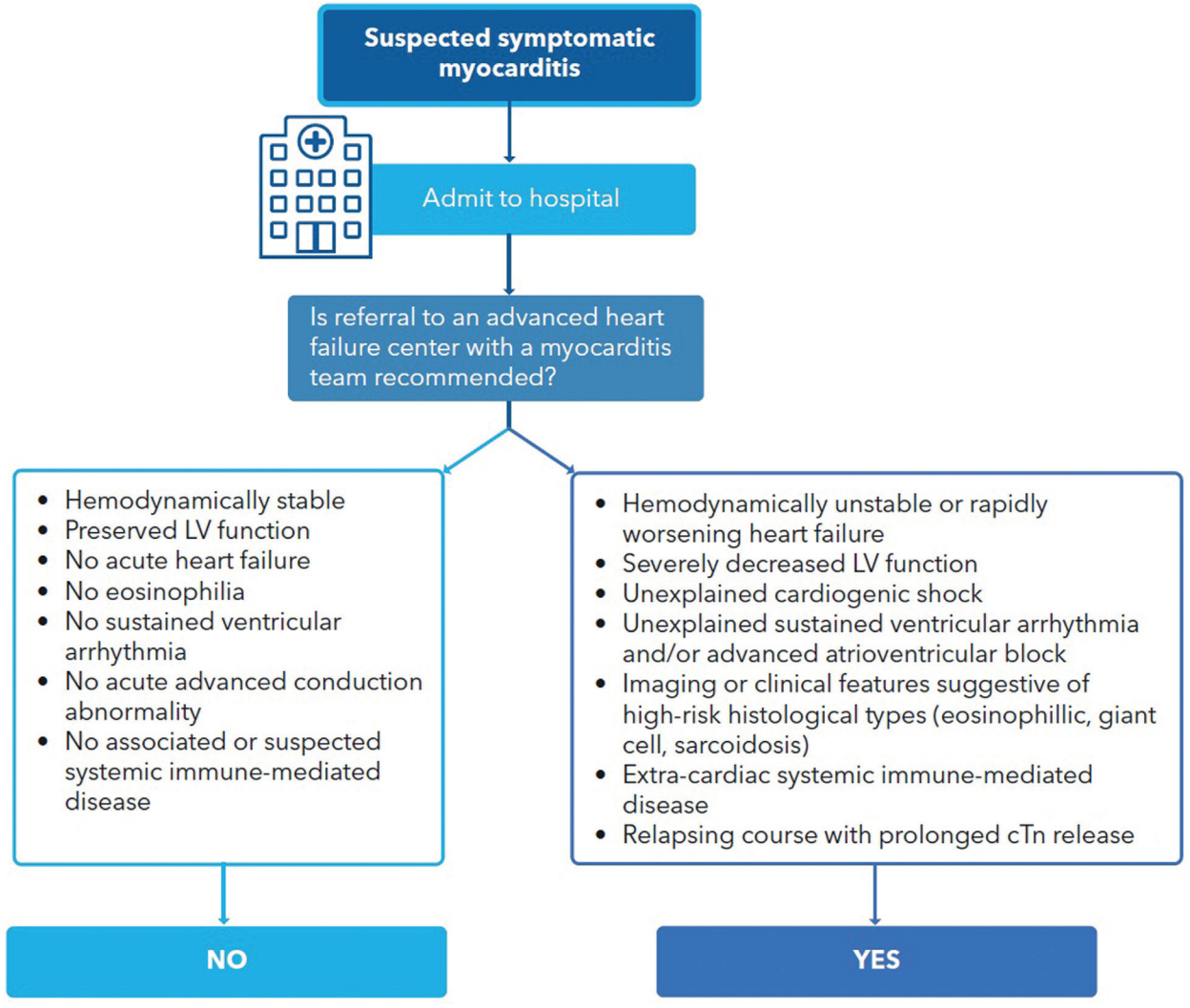
CMR = cardiac magnetic resonance; GDMT = guideline-directed management and therapy; HF = heart failure; ICU = intensive care unit; LVAD = left ventricular assist device.

context (eg, a person receiving ICI therapy vs one previously with stage C or D myocarditis who has improved to stage B myocarditis) and severity of myocardial involvement (eg, new-onset LV dysfunction). Overall management of symptomatic myocarditis includes triage to the appropriate care setting, including hospital admission and/or referral to an advanced HF center; screening and monitoring for disease progression or recurrence; an EMB as described in Section 4.4.6; treatment of etiology with consideration of steroids and other immunosuppressant agents,[140-144] as well as antiviral therapies when appropriate[80,86,87]; treatment of HFmrEF, HFrEF, and shock according to existing HF guidelines; treatment of complications, such as arrhythmia including a pacemaker as appropriate; as well as consideration of hemodynamic and mechanical circulatory support for those with stage D myocarditis. Implantable cardioverter-defibrillator implantation before discharge needs consideration in some patients. Society guidelines provided either a Class IIb recommendation (Level of Evidence: C- limited data) for those with ventricular arrhythmias leading to hemodynamic instability in the setting of GCM[4] or a Class IIa recommendation (Level of Evidence: C) irrespective of etiology.[145] The role of a wearable cardioverter-defibrillator in patients with myocarditis is uncertain in absence of supportive outcome data. Systemic anticoagulation should be initiated when a ventricular thrombus is detected. Exercise restrictions by avoiding high-intensity activity is appropriate, although patients can continue activities of daily living and should avoid excessive sedentary behavior. Genetic counseling and testing should be provided to appropriate outpatients. Patients with stage B myocarditis require repeat cardiac imaging and those with stage C or D myocarditis require repeat laboratory testing (hs-cTn and possibly other circulating biomarkers) and cardiac imaging for surveillance of resolution (see Section 4.7).

4.6.1. Triage for Need of Referral to Advanced HF Center During Index Admission

Step 2 in the 5-step care pathway for myocarditis (see **Figure 1**) requires the clinician to make the critical

FIGURE 9 Triage Factors When Considering Referral to an Advanced HF Center With a Multidisciplinary Myocarditis Team During Index Admission



cTn = cardiac troponin; LV = left ventricular.

decision about whether to refer their patient with myocarditis to an advanced HF center with a multidisciplinary myocarditis team. Features of low-risk patients that do not require referral include all the following: intact LVEF; no evidence of decompensated HF or hemodynamic instability; and no significant arrhythmias or conduction disturbances (see **Figure 9**). In contrast, those with any of the following: severe ventricular dysfunction; life-threatening arrhythmia; cardiogenic shock; refractory HF; fulminant onset; and most cases of HF/DCM with associated systemic immune-mediated disease; or suspected giant cell, eosinophilic, or sarcoid myocarditis should be referred to an advanced HF center with a multidisciplinary myocarditis team.

4.6.2. Pharmacological Treatment of Myocarditis

There is not a robust database guiding the treatment of chest pain in myocarditis or myocarditis with associated pericarditis. Pericardial-type chest pain with normal or low normal LVEF can be treated with nonsteroidal anti-inflammatory drugs and weight-adjusted colchicine.[38] Although murine models raised concern about the use of nonsteroidal anti-inflammatory drugs in myocarditis, observational studies suggest that aspirin or ibuprofen are

FIGURE 10 Key Points Regarding the Use of Immunosuppressive Therapies in Myocarditis

Not all patients with myocarditis require immunosuppressive therapy

General consensus is to administer immunosuppressive therapy for the following conditions:

- Eosinophilic myocarditis
- Giant cell myocarditis
- Granulomatous myocarditis (sarcoid)
- Associated with immune checkpoint inhibitor therapy
- In setting of other autoimmune conditions

There remains lack of broad consensus but myocarditis experts from certain centers advise:

- Perform viral PCR on endomyocardial biopsy tissue to exclude active infection prior to initation of immunosuppressive therapy
- Treat chronic lymphocytic myocarditis (with negative viral PCR) with immunosuppressive therapy

Implementation of immunosuppressive therapy

- Typically start with methylprednisolone boluses (7-14 mg/kg per day for 3 days) followed by oral prednisone taper (start at 1 mg/kg)
- Giant cell myocarditis requires higher level of immunosuppression than IV steroids, typically including a calcineurin inhibitor (cyclosporine or tacrolimus)
- Involve other specialty experts in setting of autoimmune conditions (eg, systemic lupus, vasculitis) as immunosuppressive strategy may be altered based on other organ involvement.

IVIG can be considered in the setting of inflammatory, antibody-mediated, or autoimmune disorders

IV = intravenous; IVIG = intravenous immune globulin; PCR = polymerase chain reaction.

safe in those with normal LVEF, with one case-control study showing no adverse effect on reduction of LGE via serial CMR studies.[146] Nonsteroidal anti-inflammatory drugs should be avoided in presence of symptomatic HF or shock (stage D myocarditis). Coronary spasm can complicate myocarditis with associated pericarditis,[147,148] and, when suspected, addition of a dihydropyridine calcium channel blocker would be reasonable based on extrapolation from other clinical settings.[149]

The pharmacological treatment of acute or chronic HF and arrhythmia in myocarditis should be in keeping with current guidelines for those conditions.[2-4,150-152] Beyond GDMT for HF and antiarrhythmia therapy, distinct etiology-directed therapeutic options[36,86,87,140,153] should be considered.

A particularly common question in the care of patients with acute myocarditis is when to implement immunosuppressive therapy. Key points regarding their use are summarized (see Figure 10). Immunosuppression is indicated in select patients with stage B (eg, in setting of ICI therapy) or stage C myocarditis and more with stage D myocarditis, particularly those with histologically confirmed, noninfectious immune-mediated forms such as eosinophilic myocarditis, GCM, and cardiac sarcoidosis, or with an associated systemic immune-mediated disease.[86,87,142,153] The writing committee did not reach uniform consensus, but some members felt the available evidence base, which includes the TIMIC (Tailored IMmunosuppression in virus-negative Inflammatory Cardiomyopathy) trial with chronic inflammatory cardiomyopathy,[141,142] single-center studies,[140,143,144,154,155] and one systematic review and meta-analysis,[156] supports the use of immunosuppression of select patients with lymphocytic myocarditis if the EMB sample has a negative viral PCR. Larger prospective randomized clinical trials would provide additional support for this approach. Generally, a multidisciplinary team including a clinical immunologist or rheumatologist will provide essential expertise in management of multiorgan system inflammation and mitigation of drug-related adverse event risk. Intravenous methylprednisolone boluses 7 to 14 mg/kg/d for 3 days, followed by prednisone 1 mg/kg/d orally, with subsequent tapering with steroid-sparing immunosuppressive drugs, have been associated with clinical benefit in case series.[36,86,87,142,153] In a recent large, propensity-weighted study, participants with biopsy-proven autoimmune myocarditis who received vs those who did not receive a long-term individualized immunosuppressive regimen tailored to their comorbid conditions (eg, presence of systemic immune-mediated disease) and their

disease (eg, severity of illness, histological type, and contraindication to immunosuppression), had a comparable 5-year rate of the composite outcome of death or heart transplant despite a baseline higher risk profile (including lower LVEF).[140] Patients with GCM require higher levels of immunosuppression, typically also including calcineurin inhibitors, in addition to steroids. Immunosuppression for myocarditis with coexistent inflammation in other organs may need to be adjusted to manage other organ involvement.

An ESC position statement[86] recommended that, prior to immunosuppressive therapy, viral PCR testing of the endomyocardial sample be negative for presence of viral DNA to avoid the possibility of exacerbating an active infection.[86,87,142] Indeed, studies to date[141-144,154,155] showing efficacy and safety of immunosuppression in biopsy-proven myocarditis have been done in patients with negative viral PCR on EMB. The writing committee recognizes that many centers currently do not have established protocols for viral PCR testing of endomyocardial samples; in such cases, referral to a multidisciplinary myocarditis team with this capability would be reasonable.

Antiviral therapies for viral myocarditis are evolving. Therefore, it is helpful to consult an infectious diseases or similar expert specialist for management. Antiviral therapies are an accepted alternative therapeutic approach when delivered in the context of such expert input.

Intravenous immunoglobulin may be considered in the setting of inflammatory, antibody-mediated, or autoimmune disorders. Finally, a pharmacological agent that is thought to be the trigger of the episode of acute myocarditis (eg, clozapine, ICI therapy) should be discontinued.

4.6.3. Restriction of Strenuous Physical Activity

In those with stage C and D myocarditis, patients are recommended to refrain from strenuous physical activity or competitive sports for 3 to 6 months. Whether those with stage B myocarditis should also follow those restrictions is unknown. Considerations regarding return to strenuous physical activity and competitive sports are discussed in the following text in Section 4.8.

4.6.4. Treatment of Advanced Myocarditis (Stage D)

A small segment of patients with myocarditis develops electrical or hemodynamic instability and require temporary circulatory support (TCS) or advanced therapies (durable ventricular assist device [VAD] or cardiac transplant), the latter therapies either during the acute presentation or subsequently for progressive HF. Fortunately, in the acute phase, this is relatively uncommon. In the National Inpatient Sample from 2005 to 2014, there was an increase in the presence of cardiogenic shock from 7% to 12% of patients with acute myocarditis. Although there was a parallel increase in the use of TCS from 0.16% to 1.6% of patients, the absolute rates remained low.[157] In a more recent multicenter registry of 443 patients with acute myocarditis, 4.1% required venoarterial extracorporeal membrane oxygenation (VA-ECMO), 1.1% underwent implantation of a VAD, and 0.9% heart transplantation, with overall in-hospital mortality being 2.3%.[158] Further, all of the patients who required such support (n = 118 [27%]) had at least 1 of 3 high-risk features present at admission: LVEF <50% on the first echocardiogram, sustained ventricular arrhythmias, or hemodynamic instability.

Intravenous inotropic agents, including dobutamine, milrinone, or epinephrine, may be administered for evidence of inadequate cardiac output (ie, a low-output state), but rapid hemodynamic deterioration and progression of shock is possible. Thus, patients requiring inotropic support should be transferred to advanced HF centers (Section 4.6.1). During the acute presentation, the TCS devices used most often include an intra-aortic balloon pump, intravascular axial flow device (Impella), or VA-ECMO. Given that myocarditis often is a biventricular process, VA-ECMO or other approaches that support both the RV and LV are commonly needed. TCS devices are associated with considerable risk[159] but nevertheless are required in the presence of life-threatening shock.

In the setting of myocarditis complicated by cardiogenic shock, there is a paucity of data suggesting which TCS device is preferential, a knowledge gap also present for cardiogenic shock due to other clinical conditions. Although VA-ECMO is preferentially used in patients with fulminant myocarditis for its ease of insertion and ability to provide biventricular support, short-term outcomes of patients receiving this therapy remain suboptimal. In a multicenter registry, approximately one-third of patients with fulminant myocarditis supported by VA-ECMO required a durable LVAD, transplant, or died at 90 days.[160] Likewise, a systematic review and meta-analysis of 54 observational studies involving 2,388 patients with fulminant myocarditis supported by VA-ECMO reported a short-term mortality of 35%.[161] Conversion from peripheral to central cannulation for VA-ECMO does not seem to improve outcome.[162] Prognostic factors for patients with fulminant myocarditis supported with VA-ECMO include those favorable: early administration of IVIG[163] or performance of an EMB[160]; and those unfavorable: ventricular tachycardia/fibrillation at admission, an elevated CRP, and higher peak creatine kinase-MB levels.[160,163]

Unloading of the LV via axial flow devices, such as the IMPELLA, may contribute to myocardial recovery.[164,165] Unloading is felt to reduce activation of cardiac mechano-transduction pathways, thereby reducing activation of the inflammatory cascade. Indeed, serial EMBs

demonstrated a reduction of multiple markers of inflammation, including inflammatory cellular infiltrates in the heart, in the setting LV unloading with an IMPELLA, in addition to immunosuppressive therapy.[166] Further, in that report, removal of the IMPELLA was associated with a subsequent rebound increase in markers of myocardial inflammation; however, further data, including randomized trials, if possible, are needed to confirm this intriguing hypothesis.

If patients with fulminant myocarditis supported on TCS do not recover, conversion to a durable LVAD and/or evaluation for heart transplantation should be considered.[167] In the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) of patients who received a durable LVAD from 2013 to 2016, 180 of 14,062 (1.2%) had myocarditis, and 6,602 (46.9%) had a nonischemic cardiomyopathy.[168] The duration of HF in those with myocarditis was <1 month (22%), 1-12 months (22.6%), and >1 year (55.4%). More patients with myocarditis vs nonischemic cardiomyopathy required biventricular assist devices: 15% vs 4.9%, respectively, $P < 0.01$. Although patients with myocarditis had features of higher acuity of illness at the time of VAD implantation, myocarditis was not associated with mortality in multivariable analysis (HR: 0.95; CI: 0.62-1.45; $P = 0.84$), data strongly supporting the utility of durable VADs in this setting.

Some patients with myocarditis who receive a durable VAD will subsequently recover ventricular function, even allowing explanation of the VAD. In the IMACS registry, patients with myocarditis vs nonischemic cardiomyopathy were more likely to have recovered or had their VAD explanted by 12 months though the absolute rates of such recovery were low (5% vs 1.7%).[168] The time course for VAD explanation in those with myocarditis was 6 months (0.6% of cohort), 1 year (4.4%), 2 years (11.2%), and 3 years (11.2%). Similarly, in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), of 45 adults who had their VAD explanted after a median duration of 410 days, 36% had a DCM, 32% myocarditis, 14% ischemic, and 18% miscellaneous etiologies.[169] Thus, the frequency of recovery among those with myocarditis was much higher compared with the other underlying etiologies. Specifically, 12 of 137 (9%) patients with myocarditis were explanted vs 14 of 1,009 (1.4%) with DCM and 9 of 1,294 (0.7%) with ischemic cardiomyopathy.

Cardiac transplantation is another option for patients with myocarditis who do not stabilize in the acute setting or subsequently develop progressive HF. In the United Network for Organ Sharing database of patients listed for heart transplantation, those with myocarditis were sicker as compared with those with a nonischemic or ischemic cardiomyopathy, including a higher frequency of mechanical ventilation, biventricular mechanical circulatory support and VA-ECMO use, and allosensitization. Nevertheless, their post-transplant outcomes, including rates of rejection or retransplantation and overall survival, were comparable with patients without myocarditis.[170] Likewise, a systematic review and meta-analysis showed that while a small percentage (8%) of patients with GCM were at risk of recurrence post-heart transplantation, the one and 5-year post-transplant survival rates of patients with or without GCM were comparable.[171]

4.6.5. Genetic Counseling and Testing of Patients With Myocarditis

Genetic predisposition is now firmly established to explain a subset of myocarditis cases and therefore genetic testing, much as is recommended for patients with peripartum cardiomyopathy where similar (~15%) genetic associations are known,[172] should be part of the standard workup for new diagnoses. In settings of limited resources, genetic testing could be prioritized to those with recurrent myocarditis or other risk factors for inherited cardiomyopathy (eg, as ascertained by family history) until wider capabilities are available. The genetic evaluation is ideally overseen by specialists in genetics (ie, clinical geneticist or genetic counselor) and should include collection of a 3-generation family history and molecular testing, primarily as targeted panel sequencing, including validated genes associated with cardiomyopathies and inherited arrhythmia disorders. Pretest genetic counseling requires a somewhat lengthy and detailed conversation with patients or parents and is best suited to the ambulatory setting. Because genetic results are unlikely to alter immediate management, the genetic evaluation can be performed following resolution of the acute phase (ie, posthospitalization). A positive genetic test should prompt cascade genetic testing in first-degree relatives and clinical screening for cardiomyopathy and arrhythmia in any relatives found to harbor a familial variant. This approach may afford the opportunity to deliver GDMT and thereby improve clinical outcomes in previously undiagnosed relatives. In cases when the index patient with myocarditis is found to carry a pathogenic or likely pathogenic variant, it is not known whether clinical surveillance is still needed in those relatives who test negative genetically.

4.7. Longitudinal Follow-Up of Stage B, C, and D Myocarditis

Patients with stage B myocarditis should have repeat cardiac imaging with the caveat being there are no data yet available on its utility in this newly classified stage. We advise that the follow-up imaging modality (echocardiography or CMR) be based upon the clinical context at the time of diagnosis. For example, in those with demonstrated myocardial inflammation on CMR, a repeat

CMR at 6 months would be suggested to assess for its resolution. In those with a normal LVEF and no LGE at baseline, a repeat echocardiogram, ideally with strain assessment, would be reasonable.

Patients with symptomatic myocarditis also require longitudinal follow-up of their condition. Care should not stop even if symptoms resolve in 1 to 2 weeks. Such longitudinal diagnostic studies afford the opportunity to detect persistence of myocardial inflammation and deterioration of ventricular function as well as to provide important prognostic information. Currently, there are no available evidence-based guidelines as to which tests should be acquired, and at what frequency. The following recommendations (see **Table 3**) were determined via the deliberations of the writing committee to provide needed guidance for healthcare clinicians and payers involved in the care of patients with symptomatic myocarditis.

Repeat cardiac imaging was felt appropriate at 2 time points. First, at an early interval (eg, 2-4 weeks), echocardiography can determine whether there is new or progressive deterioration of LV function, findings that would signal the possibility of a condition such as GCM. A second follow-up imaging study is advised at 6 months with the modality (echocardiography or multiparametric CMR) being based on the risk profile of the clinical presentation (low or medium/high risk). In those who are not low risk, a CMR will allow reassessment of LV function and resolution of myocardial inflammation. Further research is needed regarding treatment for patients with persistence or progression of inflammation. This approach will allow for implementation of GDMT if a reduced LVEF is newly documented and provide estimates of prognosis. In athletes wanting to return to competitive sports, the CMR can be repeated as soon as 3 months after resolution of symptoms.

TABLE 3 Longitudinal Surveillance of Stage C and D Myocarditis

Timing of Postdischarge Follow-Up and Testing	Severity of Risk	
	Low-Risk Stage C	Stage D or Medium-/High-Risk Stage C
	All the following: ■ Normal LVEF ■ No LGE ■ Hemodynamic and electrical stability	Any of the following: ■ Reduced LVEF ■ NSVT or higher-grade ventricular ectopy ■ Significant bradyarrhythmias ■ LGE on CMR ■ Increased myocardial ^{18}F-FDG uptake on PET scan ■ Hemodynamic instability/clinical heart failure
By 2-4 weeks*	■ Office visit ■ Echocardiogram†	■ Office visit ■ Biomarkers‡ ■ ECG ■ Echocardiogram†
Interval visits		■ Uptitration of GDMT for HFrEF as appropriate
6 months	■ Echocardiogram†	■ CMR§

*Those with symptomatic HFrEF ideally should be seen within 1 week of hospital discharge.
†When feasible, include assessment of strain.
‡Biomarkers include hs-troponin and natriuretic peptide level (if elevated at baseline or clinical deterioration) and CRP (if elevated at baseline, especially in context of connective tissue disease). Further biomarker testing can be based on the results at first follow-up.
§A CMR at 3 months may be preferable in athletes considering return to competitive sports.

CMR = cardiac magnetic resonance; CRP = C-reactive protein; ECG = electrocardiogram; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; GDMT = guideline-directed management and therapy; HFrEF = heart failure with reduced ejection fraction; hs = high sensitivity; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PET = positron emission tomography.

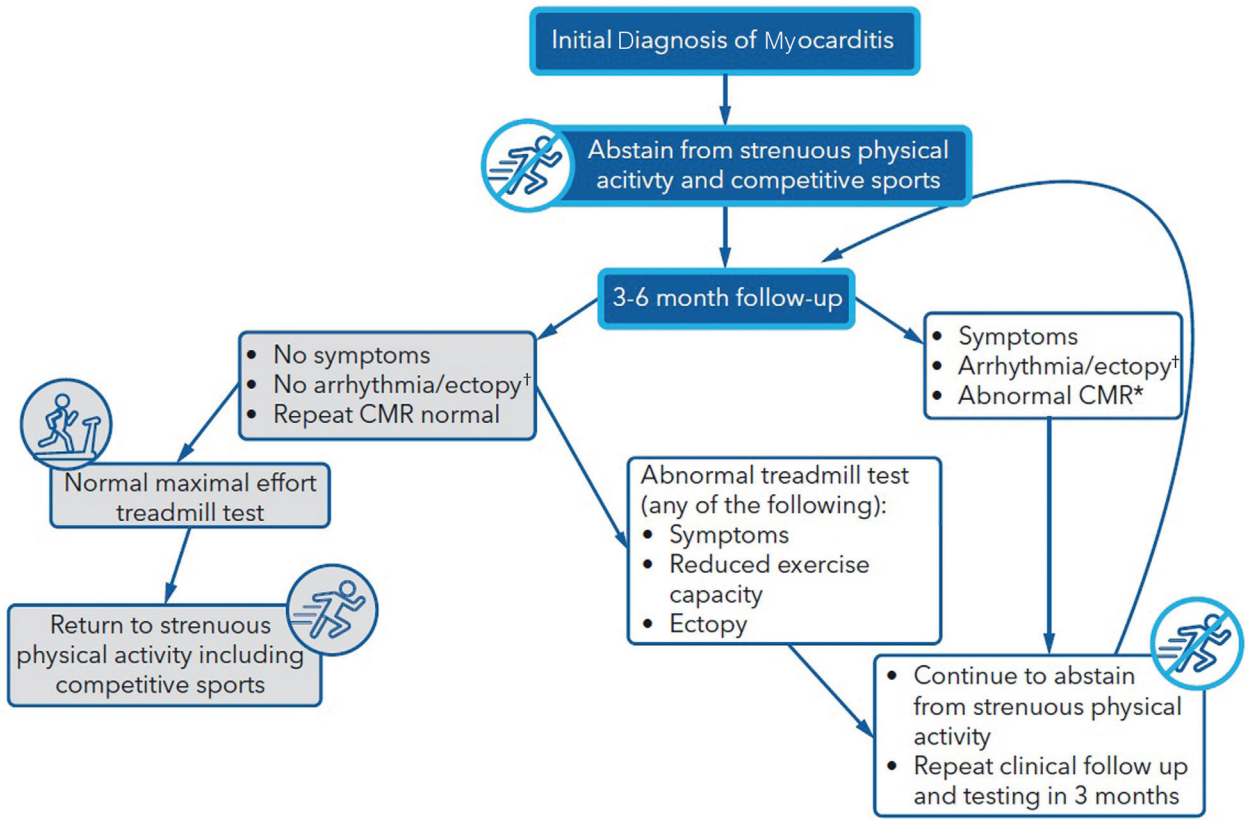
4.7.1. Longitudinal Surveillance With Imaging

In a study of 24 patients with acute myocarditis, a repeat CMR at 3 months after diagnosis was more sensitive at detecting persistent myocardial inflammation than was serial echocardiography or repeated measurement of biomarkers, including high-sensitivity Tn, CRP, and natriuretic peptides.[173] Moreover, surveillance CMR at 3 to 12 months after the acute presentation provided valuable long-term prognostic information. Most patients showed improvement in myocardial edema and reduction in LGE on follow-up CMR, but persistent or worsening LGE was an adverse prognostic indicator. In another study of 187 patients with acute myocarditis who were hemodynamically stable in the ITAMY (ITAlian Study in Myocarditis) Registry, healing (absence of edema and LGE) was present in only 11% at 6-month follow-up.[174] The subset of patients with LGE and no edema on follow-up CMR at 6 months had the worst prognosis (19 of 22 patients had cardiac events during the 7-year follow-up period), whereas patients with no LGE and no edema had the best prognosis (no cardiac events in this group). In multivariable analysis, the only independent predictors of cardiac events were a midwall septal LGE pattern on follow-up CMR (HR: 2.8; 95% CI: 1.1-7.2; $P = 0.028$) and persistence of LGE without edema on follow-up CMR (HR: 4.5; 95% CI: 1.3-14.5; $P = 0.008$). Others have demonstrated the prognostic value of serial changes of LGE.[173,175,176]

Myocardial T_1 and T_2 relaxation times may remain elevated on follow-up CMR after normalization of other parameters, such as T_2 ratio, EGE ratio, and ECV fraction; however, the prognostic significance of such findings remains unclear.[175] Among patients with nonfulminant acute myocarditis and normal LVEF on initial CMR, reduction in LVEF on follow-up CMR is uncommon[139,158] but should prompt further evaluation if present.

Although the role of serial ^{18}F-FDG PET imaging in determining adequate response to treatment in patients with cardiac sarcoidosis is well documented,[74] the same evidence base does not exist for patients with myocarditis. Serial ^{18}F-FDG PET imaging, if pursued, should be performed with a similar patient preparation as used in the initial scan leading to the diagnosis of myocarditis.

FIGURE 11 Recommendations for Abstinence From Strenuous Physical Activity and Return to Competitive Sports Following Diagnosis of Myocarditis



*An abnormal CMR includes any of the following: reduced LVEF or RVEF; or evidence of nonischemic inflammation as described previously, including presence of LGE. †Assessed by 24-hour electrocardiographic monitoring. CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.

4.7.2. Longitudinal Surveillance With Biomarkers

Circulating hs-cTn levels should be followed sequentially in a patient with symptomatic myocarditis. For those with elevated natriuretic peptide levels at baseline, serial measurement to document improvement is reasonable. As described previously, CMR has greater utility for monitoring myocardial inflammation than does biomarkers. Nevertheless, the significantly lower cost and ease in obtaining biomarkers, particularly hs-cTn, is such that they can be obtained more frequently and could alert clinicians to subclinical deterioration, which would prompt reassessment of ventricular function by echocardiography or even an early CMR to reassess the degree of myocardial inflammation and injury. In a very small study of patients with myocarditis related to ICIs, higher cTnI and creatine kinase-MB at presentation correlated with progression to severe myocarditis.[177] Delineating potential autoantigens that could be used as circulating biomarkers would be useful mechanistically and potentially helpful for tracking severity or changes in status.

4.8. Return to Strenuous Physical Activity, Including Competitive Sports

Although existing literature on this subject is limited, the prevailing suggestion is to resume exercise 3 to 6 months following myocarditis, provided that symptoms have resolved (see **Figure 11**).[178-181] At that time, it is advisable to obtain either a CMR (stage D or ≥ medium-risk stage C myocarditis) or transthoracic echocardiography (low-risk stage C myocarditis), a 24-hour ECG, and an exercise stress test to evaluate for stress-induced arrhythmias.[180] If all these examinations are unremarkable and the patient is asymptomatic, we consider it safe to resume exercise.[178-181]

Due to an increased risk for recurrence and silent clinical progression of the disease, athletes with previous myocarditis should undergo a periodic reassessment, particularly within the first 2 years.[181]

4.9. Knowledge Gaps and Future Directions

4.9.1. Need for Registries and Further Research

The COVID-19 pandemic demonstrated the feasibility of a rapid and effective establishment of global scientific collaboration, as myocarditis emerged as a significant public health issue worldwide. With the foundation of these networks, the way was paved to strengthen international collaborations in the future and pursue our shared objective—improved care for patients with myocarditis.

International registries for myocarditis are necessary to gather data on a larger scale that enables detection of characteristics and patterns of myocarditis that would not be recognized in single-center studies. A shared international definition of myocarditis with similar diagnostic standards will be paramount to allow for comparability of data.[35]

Registry data will help to obtain in-depth understanding of common patterns in pathophysiology, to discover risk predictors, to learn about the clinical course based on various treatment approaches, and to identify novel trends early—for example, if a novel virus is spreading in a population,[182] or if myocarditis develops as a side effect of a novel therapy.[183]

At least as important as establishing international registries will be multicenter clinical trials, when novel therapies are tested. Because of the heterogeneity of the patient population, innovative trial methods, including adaptive design or precision medicine approaches, should be considered. Most therapies had been tested in small single-center studies that did not provide sufficient evidence for clinical guidelines.[141,143,144,154,155,158,184-188] Due to the absence of standardized therapy guidelines, myocarditis treatment varies significantly among national and international centers. To enhance patient care, it is essential to establish uniform treatment protocols, enabling the collection of large-scale therapy response data for further refinement and optimization of treatment options.

Partnerships with industry, academic centers, and patient advocacy groups are needed to successfully complete multicenter, international registries for the study of myocarditis. Decentralized structures for enrollment coupled with specialized centers for clinical research should be considered in the formation of such registries.

There is a critical need for future research on prevention and cardioprotection; surveillance in patients at risk for myocarditis; diagnostic strategies, including circulating biomarkers, imaging, microRNAs, other omics, genetics, histopathology, and immunology; elucidating mechanisms and pathophysiology; predictors of outcomes and prognosis; appropriate treatment strategies; surveillance for recovery and recurrence; and monitoring of myocarditis. Additional studies are needed to define contributions of genetic background and immune phenotype as risk modifiers for myocarditis; how and when does genetic testing improve classification, modify management, inform future risk of recurrent cardiac inflammation, and/or stratify risk for both myocarditis and related disease (ie, cardiomyopathy) in relatives.

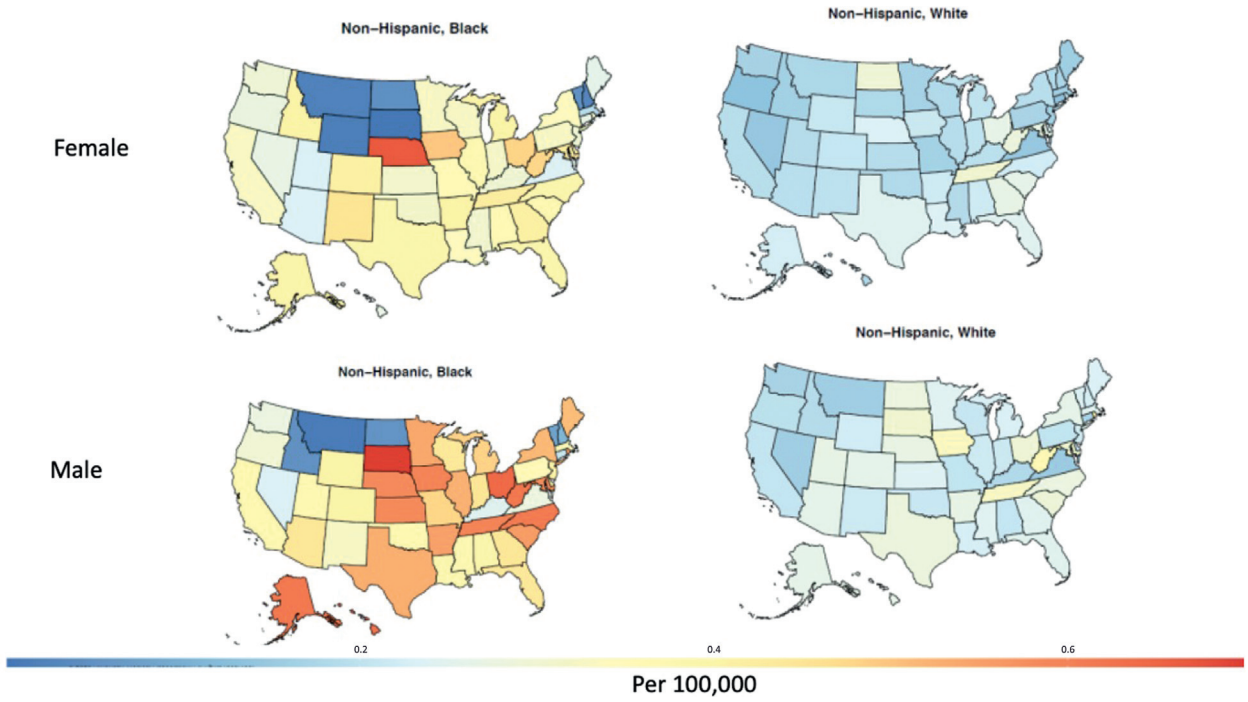
There is also a critical need to capture myocarditis as a diagnosis. The International Classification of Diseases-Tenth Revision code may not be used in cases that are missed or not hospitalized; thus, there may be gross under-reporting. Furthermore, proximate causes such as severe COVID-19 infection, cancer that requires ICI therapy, or systemic lupus may be the primary diagnosis and myocarditis may or may not be captured as a secondary diagnosis. Therefore, defining the epidemiology of myocarditis, including the true incidence and prevalence, geographic, and secular variation of myocarditis, mortality, and outcomes related to myocarditis, needs further study.

The psychosocial, socioeconomic, and healthcare burden of the diagnosis of myocarditis, including depression and anxiety, are considerable in both patients and their caregivers, particularly because young and often previously active individuals are affected. Long-term follow-up found that up to one-third of patients with fulminant myocarditis requiring mechanical circulatory support had severe anxiety or depressive symptoms and were at risk for post-traumatic stress disorder.[189] This burden has not been systematically measured or consistently addressed in current practice. Individuals may not be able to resume physical activity, sports, or return to work that may entail physical labor. Economic burden at the individual or healthcare level has not been studied and requires further research.

4.9.2. Need for Improved Phenotyping: Immuno-Metabolic Imaging

The ability to directly image the immune system and cellular activity would vastly improve the phenotyping of myocarditis. Advanced cardiac imaging modalities, such as PET and CMR, to image the molecular inflammatory response, immune cell types, and metabolic activity for phenotypic signatures,[190,191] offers promise to enhance diagnostic testing and risk stratification as well as allowing more targeted therapy. Emerging PET radiotracers and molecular targets for imaging myocarditis include ^{68}Ga-DOTATATE (targeting somatostatin receptors expressed on proinflammatory macrophages), and ^{18}F- and ^{68}Ga-based tracers (targeting the folate receptor beta-isoform expressed on activated macrophages).[190,192] In MRI, tissue-resident macrophage activity and cellular inflammation can be detected by ultrasmall superparamagnetic

FIGURE 12 State-Level Age-Standardized Mortality Rates for Myocarditis in 2019



Adapted with permission from Johnson et al.[221]

particles of iron oxide,[193] neutrophil and monocyte activity by myeloperoxidase-activated gadolinium chelate in preclinical studies,[194] and monocytes by intravenous ^{19}F-enhanced CMR-perfluorocarbon-containing nanoparticles.[195] Clinical hyperpolarized MRI can image key metabolites of inflammation, such as hyperpolarized carbon-13 pyruvate and carbon-13 lactate.[191]

4.9.3. Need for Improved Phenotyping: Circulating Biomarkers

In addition to cTn, several novel circulating biomarkers are currently being investigated for their potential role in improving the diagnosis and phenotyping of myocarditis. These biomarkers aim to enhance diagnostic accuracy, risk stratification, treatment monitoring, and outcome prediction in myocarditis. Serum organ-specific antiheart autoantibodies to myosin heavy chain and other autoantigens (ie, antinuclear autoantibodies) are established biomarkers for biopsy-proven autoimmune myocarditis. These biomarkers are evident in both organ-specific myocarditis and myocarditis in the context of systemic immune-mediated diseases, serving as predictors of a worse prognosis, especially at high titers.[101,196,197] Cellular immune-phenotype biomarkers have also been reported.[198,199] Others are being studied; galectin-3, soluble suppression of tumorigenicity 2 (sST2), and specific microRNAs (miRNAs) have shown promise in their association with myocarditis. Galectin-3 has been associated with cardiac remodeling and poor prognosis in HF.[200] A study in chronic Chagas disease cardiomyopathy caused by *Trypanosoma cruzi* infection suggests that galectin-3 plays a significant role in inflammation and fibrosis, and its expression in human hearts associates with myocarditis in Chagas cardiomyopathy.[201,202] ST2, a member of the interleukin-1 receptor family, is involved in cardiac remodeling and fibrosis. Elevated levels of sST2 have been associated with myocardial stress and adverse outcomes in various cardiac conditions. In the context of myocarditis, ST2 levels may provide valuable information about disease severity and prognosis.[203]

miRNAs, small noncoding RNA molecules, have been emerging as a prominent but controversial area of research with an ever growing number of miRNAs, alone or in combination (eg, miR-221/222,[204] miR-155,[205,206] miR-10a*,[207] miR-142,[208] and miR-590-3p,[209] miR21/miR30a-5p,[210] miR-548a-3p/miR-500b-5p[211], and miR-Chr8:96/miR-155/miR-206[212] being associated or proposed

FIGURE 13 Social Determinants of Health Related to Myocarditis

to be associated with myocarditis. Importantly, care is required to carry out experiments in humans and ensure that the miRNA homologs are feasible in human (eg, miR-721[213] with its putative human homolog).[214,215] It is also important to ensure disease specificity, as many microRNAs are also expressed in other cardiomyopathies.[216,217] Finally, although some may distinguish,[210] all have yet to be validated in a large, well-defined clinical cohort. Thus, to date, there is no validated miRNA alone or a set of miRNAs that is specific and reliable to distinguish myocarditis, limiting their present diagnostic value.

In summary, to achieve a more accurate and etiology-specific diagnosis of myocarditis, it is essential to ensure disease-specificity and carry out validation alone or as part of a combination of multiple biomarkers (with cTn) and incorporate them into comprehensive diagnostic algorithms that consider clinical evaluation, imaging studies, and other relevant parameters.

4.9.4. Need for Improved Phenotyping: Biopsy

Despite the valuable framework for the histopathologic diagnosis provided first by the Dallas criteria[218] and then the ESC criteria,[86] as well as IHC and viral PCR testing, homogenous reporting is not consistently used across different regions/countries or even among pathologists in the same country.

Although no major issues are present in the setting of eosinophilic, polymorphous, granulomatous, and GCM, the real diagnostic challenge is with lymphocytic myocarditis. The existing cutoff of ≥14 leukocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of ≥7 CD3 T-lymphocytes/mm^2, without any specification of

distribution, should be revised. A recent survey on EMB practice for myocarditis highlighted the clinically unmet need to update and standardize the current diagnostic criteria.[88,219,220] The following crucial issues include: 1) the histopathological diagnosis (the extent/grading and type of inflammation; whether myocyte injury is always required; and the role of fibrosis); 2) the need of IHC (when and which panel, especially when the infiltrates are of mononuclear cells, such as lymphocytes and macrophages, which cannot be distinguished clearly by histology); and 3) the use of molecular pathology for infectious agents.

4.9.5. Need to Be Aware of Racial Differences

The age-standardized mortality rates for myocarditis in the United States are higher in Black people than White people, both in women and men (**Figure 12**).[221] Efforts to increase awareness of this condition in those at higher risk from myocarditis are needed.

4.9.6. Needs for Consideration of Social Determinants of Health

There is inequity in access to screening, evaluation, and treatment of myocarditis. Underinsured/not insured patients, patients with low income, people of color, and patients living in rural areas may not be referred for screening, imaging, testing, and or advanced therapies. Contemporary diagnoses of myocarditis rely heavily on the use of CMR; however, uptake of this technology is heterogeneous and variation in use as well as wait times present concerns for equity of provision.[222] More widespread and equitable genetic testing in myocarditis is desired, given that currently there appears to be lower clinical testing rates in Black populations as well as higher genetic diversity in individuals of African ancestry.[223] Genomic studies in diverse and inclusive populations should be a priority for further myocarditis research. Because social determinants of health have been implicated in altered immunity and inflammation,[224] it stands to reason that these variables may impact the course and outcome of myocarditis (**Figure 13**). Further research is needed to understand the intersection between clinical variables, genetic risk, and social determinants of health in myocarditis outcomes.

4.9.7. Need for Access and Coverage for Screening, Diagnostic Evaluation, and Care

There is inadequate healthcare coverage for myocarditis care. Many patients are not covered for repeat imaging and/or testing following myocarditis diagnosis or initial testing with advanced imaging in the outpatient setting. Patients may require repeat diagnostic evaluation to ascertain resolution of abnormal cardiac involvement and/or for consideration of additional therapies, such as GDMT for cardiomyopathy or HF if they have persistent symptoms and or cardiac dysfunction. There also is a great need for advocacy, health policy, and interventions for equity for a disease such as myocarditis, that requires advanced therapies when severe.

PRESIDENT AND STAFF

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KEY WORDS **ACC Expert Consensus Decision Pathway, arrhythmia, cardiac, chest pain, genetics, heart failure, immunosuppression, inflammation, magnetic resonance imaging, myocarditis, sports**

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2024 ACC EXPERT CONSENSUS DECISION PATHWAY ON STRATEGIES AND CRITERIA FOR THE DIAGNOSIS AND MANAGEMENT OF MYOCARDITIS

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mark H. Drazner *(Chair)*	UT Southwestern Medical Center—Clinical Chief of Cardiology; James M. Wooten Chair in Cardiology	None	None	None	None	None	None
Biykem Bozkurt *(Vice Chair)*	Baylor College of Medicine and DeBakey VA Medical Center—Senior Dean of Faculty, Medical Care Line Executive, Gordon Cain Chair, Professor of Medicine	■ Abiomed ■ Johnson & Johnson ■ Roche	None	None	None	■ Abbott Laboratories* ■ AstraZeneca Pharmaceuticals ■ Respicardia/Zoll	None
Leslie T. Cooper *(Vice Chair)*	Alix School of Medicine at Mayo Clinic—Elizabeth C. Lane, PhD, and M. Nadine Zimmerman, PhD, Professor of Medicine Mayo Clinic, Division of Cardiovascular Disease	■ Bristol Myers Squibb Company* ■ Cantargia ■ Cardiol* ■ Kiniksa	None	None	■ Moderna (DSMB)	■ Stromal Therapeutics* ■ The Myocarditis Foundation†	None
Niti R. Aggarwal	Mayo Clinic—Assistant Professor of Medicine Consultant, Department of Cardiovascular Disease	None	None	None	None	None	None
Cristina Basso	University of Padua—Professor of Pathology	None	None	None	None	None	None
Nicole M. Bhave	University of Michigan Medical School—Associate Professor of Cardiovascular Medicine	None	None	None	None	None	None
Alida L.P. Caforio	University of Padua—Department of Cardiac, Thoracic, Vascular Sciences and Public Health Associate Professor of Cardiology	None	None	None	None	None	None
Vanessa M. Ferreira	University of Oxford—Professor of Cardiovascular Medicine	None	None	■ Patent-Method and apparatus for enhancing medical images† ■ Patent-Method and apparatus for quality prediction† ■ Patent-Method for identity validation and quality assurance of quantitative magnetic resonance imaging protocols†	■ GE Healthcare*	None	None
Bettina Heidecker	Deutsches Herzzentrum der Charité Berlin, Universitätsmedizin —Head of Heart Failure and Cardiomyopathy	■ AstraZeneca ■ Pfizer	None	■ Patent-Inventor on patents that use RNA for diagnosis of myocarditis†	■ Pfizer†	None	None
Amy R. Kontorovich	Icahn School of Medicine at Mount Sinai—Associate Professor of Medicine in Cardiology and Genomic Medicine	■ Alexion ■ AstraZeneca	None	None	None	None	None
Pilar Martín	National Cardiovascular Research Center—Assistant Professor	None	None	None	None	None	None
Gregory A. Roth	University of Washington School of Medicine—Associate Professor	None	None	None	None	None	None
Jennifer E. Van Eyk	Cedar Sinai Medical Center—Professor	None	None	None	■ Abbott*	None	None

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*Significant relationship.
†No financial benefit.

ACC = American College of Cardiology; DSMB = Data Safety and Monitoring Board; UT = University of Texas.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2024 ACC EXPERT CONSENSUS DECISION PATHWAY ON STRATEGIES AND CRITERIA FOR THE DIAGNOSIS AND MANAGEMENT OF MYOCARDITIS

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Amrut Ambardekar	Content Reviewer—ACC Expert	University of Colorado—Associate Professor of Medicine, Cardiology	None	None	None	None	■ ATTRIBUTE-CM Trial* ■ CardioTransform Study*	None
Robert Baeten	Official Reviewer—ACC Cardiovascular Team Council	Piedmont Hospital—Clinical Assistant Professor	None	None	None	None	None	None
Sanjay Divakaran	Official Reviewer—ACC Imaging Council	Brigham and Women's Hospital—Director, Cardiac Sarcoidosis Program; Associate Director, Nuclear Cardiology	■ Kinevant	None	None	None	None	None
Perry M. Elliott	Content Reviewer—ACC Expert	University College London—Professor of Cardiovascular Medicine	■ BioMarin ■ Cardior ■ Cytokinetics ■ DiNAQOR† ■ Pfizer‡ ■ Sanofi/ Genzyme	■ Peer View ■ Peer Voice† ■ Radcliffe Medical	None	■ Sarepta‡	■ Cardiomyopathy UK† ■ European Society of Cardiology† ■ EXPLORER-HCM* ■ International Cardiomyopathy Network† ■ REALM-DCM*	None
James C. Fang	Content Reviewer—ACC Expert	University of Utah School of Medicine—Chief of Cardiovascular Medicine	None	None	None	■ Boehringer Ingelheim (DSMB) ■ Capricor (DSMB) ■ National Institutes of Health ■ Windtree (DSMB)	■ ACI Clinical ■ AHA ■ Amgen ■ AstraZeneca ■ HFSA ■ National Institutes of Health ■ Novartis ■ Sardocor ■ University of Utah ■ UpToDate	None
Nisha Aggarwal Gilotra	Content Reviewer—ACC Expert	Johns Hopkins Hospital—Director, Cardiac Sarcoidosis Program; Associate Professor of Medicine	■ Kiniksa	None	None	None	None	None
Dharam J. Kumbhani	Official Reviewer—ACC Solution Set Oversight Committee	UT Southwestern—Professor of Medicine; Section Chief, Interventional Cardiology	None	None	None	None	■ ACC ■ Circulation‡	None
Peter P. Liu	Content Reviewer—ACC Expert	University of Ottawa Heart Institute—Chief Scientific Officer; Vice President of Research	None	None	None	■ Canadian Institutes of Health Research‡ ■ Genome Canada† ■ Roche Diagnostics‡ ■ Servier†	■ Servier	None
Valentina Puntmann	Content Reviewer—ACC Expert							

Continued on the next page

APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nosheen Reza	Content Reviewer—ACC Expert	University of Pennsylvania—Assistant Professor of Medicine	■ Bristol Myers Squibb† ■ Knowledge to Practice ■ Med Learning Group ■ Medscape ■ Physicians' Education Resource ■ Roche ■ ZOLL	None	None	■ Cytokinetics† ■ National Institutes of Health†	■ ACACIA-HCM* ■ BAG3-DCM* ■ DISCOVER-HCM* ■ EMBARK-HFpEF* ■ Exploratory Study of Danicamtiv in Patients With Primary Dilated Cardiomyopathy (DCM) Due to Genetic Variants* ■ FOREST-HCM* ■ GENETIC-DCM* ■ MAPLE-HCM* ■ MERCUTIO* ■ REDWOOD-OLE* ■ SEQUOIA-HCM*	None

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†Significant relationship.

‡No financial benefit.

ACC = American College of Cardiology; AHA = American Heart Association; DSMB = Data Safety and Monitoring Board; HFSA = Heart Failure Society of America.

APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
AHA = American Heart Association
AV = atrioventricular
CD = cluster of differentiation
CMR = cardiac magnetic resonance
CRP = C-reactive protein
CT = computed tomography
cTn = cardiac troponin
cTnI = cardiac troponin I
cTnT = cardiac troponin T
DCM = dilated cardiomyopathy
ECDP = expert consensus decision pathway
ECG = electrocardiogram
ECV = extracellular volume
EGE = early gadolinium enhancement
ECMO = extracorporeal membrane oxygenation
EMB = endomyocardial biopsy
ESC = European Society of Cardiology
^{18}F-FDG = ^{18}F-fluorodeoxyglucose
GCM = giant cell myocarditis
GDMT = guideline-directed management and therapy
HF = heart failure
HR = hazard ratio
HFrEF = heart failure with reduced ejection fraction
hs-cTn = high-sensitivity cardiac troponin
ICI = immune checkpoint inhibitor
IHC = immunohistochemistry
LGE = late gadolinium enhancement
LV = left ventricle
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
miRNA = microRNA
MRI = magnetic resonance imaging
PCR = polymerase chain reaction
PET = positron emission tomography
TCS = temporary circulatory support
Tn = troponin
VA-ECMO = venoarterial extracorporeal membrane oxygenation
VAD = ventricular assist device