Circulation

AHA SCIENTIFIC STATEMENT

Recognition and Initial Management of Fulminant Myocarditis

A Scientific Statement From the American Heart Association

Endorsed by the Heart Failure Society of America and the Myocarditis Foundation.

ABSTRACT: Fulminant myocarditis (FM) is an uncommon syndrome characterized by sudden and severe diffuse cardiac inflammation often leading to death resulting from cardiogenic shock, ventricular arrhythmias, or multiorgan system failure. Historically, FM was almost exclusively diagnosed at autopsy. By definition, all patients with FM will need some form of inotropic or mechanical circulatory support to maintain end-organ perfusion until transplantation or recovery. Specific subtypes of FM may respond to immunomodulatory therapy in addition to guideline-directed medical care. Despite the increasing availability of circulatory support, orthotopic heart transplantation, and disease-specific treatments, patients with FM experience significant morbidity and mortality as a result of a delay in diagnosis and initiation of circulatory support and lack of appropriately trained specialists to manage the condition. This scientific statement outlines the resources necessary to manage the spectrum of FM, including extracorporeal life support, percutaneous and durable ventricular assist devices, transplantation capabilities, and specialists in advanced heart failure, cardiothoracic surgery, cardiac pathology, immunology, and infectious disease. Education of frontline providers who are most likely to encounter FM first is essential to increase timely access to appropriately resourced facilities, to prevent multiorgan system failure, and to tailor disease-specific therapy as early as possible in the disease process.

Robb D. Kociol, MD, MS, Chair
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Daniel B. Sims, MD, FAHA
Gaetano Thiene, MD, FAHA
Orly Vardeny, PharmD, MS, FAHA
On behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology

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Fulminant: adjective
ful·mi·nant | \ 'fůl-mə-nənt, 'fəl-
coming on suddenly with great severity.
fulminant hepatitis with total hepatocyte necrosis

C.L. Humberston et al[1]

As the definition of fulminant above suggests, fulminant myocarditis (FM) comes on suddenly and often with significant severity, resulting in an exceptionally high risk of death caused by cardiogenic shock, fatal ventricular tachyarrhythmias, or bradyarrhythmia. However, in the present day, with our ability to fully support a patient's circulation (and oxygenation/ventilation when necessary), the early recognition of FM, institution of circulatory support, and maintenance of end-organ function (especially avoiding prolonged neurologic hypoxemia) can result in favorable outcomes among conditions that were previously almost universally fatal.[2] In some subtypes, appropriate immunosuppression therapy and monitoring can induce remission. In others, if the circulation is supported, spontaneous recovery without specific treatment for inflammation is possible.[3] A good working definition of FM is a sudden and severe inflammation of the myocardium resulting in myocyte necrosis, edema, and cardiogenic shock. It is important to distinguish FM from other forms of acute circulatory compromise, the most common being an acute coronary syndrome.

This statement is meant to educate frontline healthcare providers to consider and identify FM at its earliest stages using the most relevant advanced diagnostic modalities in order to provide treatment as soon as possible. In many cases, stabilization and transfer of such patients to centers that have the capacity and experience to manage patients with FM is essential.

PRESENTING SIGNS AND SYMPTOMS

Clinical presentations vary widely, with or without systemic manifestations of an infection or inflammatory disorder. In the European Study of Epidemiology and Treatment of Inflammatory Heart Disease of 3055 patients,[4] most of those screened had dyspnea followed by chest pain and arrhythmias such as atrial fibrillation, ventricular tachycardia, or heart block. It may present as sudden death and is considered an important diagnostic consideration by the American College of Cardiology and American Heart Association (AHA) for sudden death in competitive athletes.[5] Cardiogenic or mixed cardiogenic and distributive shock may develop rapidly, often soon after first medical contact. In one of the most comprehensive clinicopathological descriptions of myocarditis, investigators from Johns Hopkins were among the first to report the paradoxical complete recovery of patients with FM if the patients were able to survive the acute hemodynamic collapse.[6] The fulminant presentation may be a marker of a more robust immunological/inflammatory response indicative of more effective viral clearance and thus predictive of eventual complete myocardial recovery, at least among those with an infectious myocarditis. Children and women may be more susceptible to this dramatic presentation. Other medical disorders such as lupus and celiac sprue may be concomitantly present and likely play a direct role in the pathogenesis of the myocardial inflammation, either alone or in concert with a propensity toward specific viral insults.

LABORATORY EVALUATION IN MYOCARDITIS

The ECG in FM may demonstrate low QRS voltage[7] because of myocardial edema; rarely, there is evidence for left ventricular (LV) hypertrophy.[8] Electrocardiographic signs of an injury current with ST-segment elevations in contiguous leads in a segmental fashion are not uncommon and may mimic coronary occlusion.[9] A nonvascular distribution of ST-segment elevations is common in FM but should not delay angiographic assessment of the coronary anatomy. Concomitant evidence for pericarditis with PR-segment depression may also be present. Frequent ectopy, ventricular arrhythmias, and conduction abnormalities are likewise common.

Although an elevated serum cardiac troponin (cTn) is almost always present in FM, there should be a low threshold for evaluation with coronary angiography because acute coronary syndrome is the most common cause of a cardiac presentation with elevated biomarkers. However, an absence of cTn increase does not rule out myocarditis.[10] Cardiac biomarkers in FM can reach levels similar to those in patients with transmural infarctions caused by epicardial coronary occlusions. Experimental and clinical studies suggest that serum cTn can be a useful diagnostic tool early in the course of myocarditis.[11,12] In a registry cohort of 386 patients with myocarditis and preserved LV ejection fraction (LVEF), increased cTn was found in all 386 patients (100%); 385 patients (99%) had abnormal values of erythrocyte sedimentation rate or C-reactive protein.[13] Levels of biomarker elevation were similar in patients with and those without adverse cardiac events in follow-up. In a study from the endomyocardial biopsy (EMB) database at Johns Hopkins Hospital, a wide range of cTn values were associated with giant cell myocarditis (GCM), but the investigators did not find a significant correlation between the magnitude of cTn measured and patient prognosis.[14] Natriuretic peptides are often elevated and may be useful prognostically. The European Society of Cardiology (ESC) position statement on the management of acute myocarditis recommends the assessment

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of serum cTn, erythrocyte sedimentation rate, and C-reactive protein to aid in the diagnosis of myocarditis.[15] However, a normal erythrocyte sedimentation rate and C-reactive protein level do not exclude myocarditis.[16] Routine viral serologies are not recommended because of a lack of sensitivity and specificity compared with viral genome polymerase chain reaction performed on endomyocardial tissue obtained by biopsy.[15]

The emergency department and outpatient diagnosis of FM has several diagnostic pearls and potential pitfalls (partially listed in Table 1) that should be kept in mind by frontline providers in the outpatient setting.

Unique Diagnostic and Management Issues During Hospital Admission for FM: Roles for Multimodality Imaging and EMB

Echocardiography

Because of rapid and portable acquisition, echocardiography remains the first test in most cases of FM, with the ability to rapidly process a wide differential diagnosis (including pericardial disease) and to assess cardiac and valvular function and morphology. Early use of echocardiography is essential to establish a diagnosis and the severity of cardiovascular compromise. Apart from cardiac dysfunction and its sequelae (eg, thrombus), several echocardiographic features may characterize FM (reviewed by Skouri and colleagues[18]), including normal LV diastolic dimension with increased wall thickness resulting from myocardial edema[8,18–20] and pericardial effusion.[21] Several studies suggest that increased LV wall thickness may be a dynamic pathophenotype with gradual resolution over time.[8,19] Classically, greater ventricular dilatation may suggest a chronic insult, with a smaller LV more consistent with a fulminant pathogenesis. Segmental LV dysfunction, diastolic dysfunction, right ventricular dysfunction, and cardiac thrombus can also occur.[22] Finally, sensitive indicators of systolic and diastolic function such as tissue Doppler imaging[20] and strain imaging[23] are often abnormal in myocarditis, although there is likely to be overlap between acute and chronic cardiomyopathies in these indexes that limit their diagnostic specificity.

Although the primary role for echocardiography in myocarditis is in diagnosis and surveillance, several echocardiographic parameters have proven useful in delineating recovery. Patients with FM experience a greater degree of recovery in contractile function if they survive to recovery relative to those with acute myocarditis.[8] In children, both smaller LV dimension[24] and greater LV thickness[25] are associated with improved outcomes. As in all types of heart failure, the presence of right ventricular dysfunction[18] and persistent diastolic dysfunction[26] are poor prognostic features.

Table 1. Potential Pearls and Pitfalls in the Evaluation and Early Management of FM

Diagnosis	Consider myocarditis in young patients with apparent cardiovascular conditions often presenting as more common conditions such as ACS or de novo AHF.
	Young patients without typical cardiovascular risk factors and history of signs and symptoms of recent viral URI or enteroviral infection presenting with cardiovascular symptoms.
	Any patient with shock, electric instability, or rapidly evolving conduction abnormalities such as widening of the QRS complex or PR prolongation.
	Recognize typical signs and symptoms of RHF such as RUQ pain, LFT abnormalities, jaundice, elevated neck veins, peripheral edema, hepatomegaly with liver pulsatility. Distinguish RHF from primary hepatobiliary disease such as cholecystitis early before progressive cardiogenic shock.
Triage	Early recognition of circulatory compromise such as a narrow arterial pulse pressure, sinus tachycardia, cool or mottled extremities, or elevated lactate. Patients may present febrile secondary to severe inflammation. Although the more common diagnosis is infection and sepsis, this may also be severe myocarditis. Discriminating sepsis from early cardiogenic shock secondary to myocarditis is challenging during the early stages of workup and treatment. A high index of suspicion is warranted.
Initial management	Avoid treatment of sinus tachycardia with rate control agents (especially those with negative inotropic properties such metoprolol, diltiazem, or verapamil). Among patients with systolic dysfunction, cardiac output may significantly depend on a compensatory increase in heart rate given a minimal ability to augment stroke volume in the acutely affected nondilated heart. Consider hypersensitivity myocarditis, a subset of eosinophilic myocarditis, generally presenting as FM with peripheral eosinophilia (65% of patients), rash, or elevated LFTs. Patients often will have a fever and high risk (43%) of death, transplantation, or VAD placement at 120 d. An EMB is often necessary for definitive diagnosis. Common causative agents are antibiotics such as β-lactams and minocycline and certain central nervous system drugs such as clozapine and carbamazepine.[17] Avoid NSAIDs because they may increase Na retention, cause myocardial harm, and exacerbate renal hypoperfusion.

ACS indicates acute coronary syndrome; AHF, acute heart failure; EMB, endomyocardial biopsy; FM, fulminant myocarditis; LFT, liver function test; NSAID, nonsteroidal anti-inflammatory drug; RHF, right-sided heart failure; RUQ, right upper quadrant; URI, upper respiratory infection; and VAD, ventricular assist device.

Cardiac Magnetic Resonance Imaging

In addition to suggestive functional and morphological features (eg, right ventricular and LV size and function, pericardial effusion), gadolinium contrast-enhanced cardiac magnetic resonance (CMR) affords unique insights into tissue-level pathologies consistent with myocarditis, including myocardial edema and fibrosis (eg, T2- and T1-weighted sequences and late gadolinium enhancement [LGE]).[27,28] Traditional consensus guidelines (Lake Louise criteria) have recommended

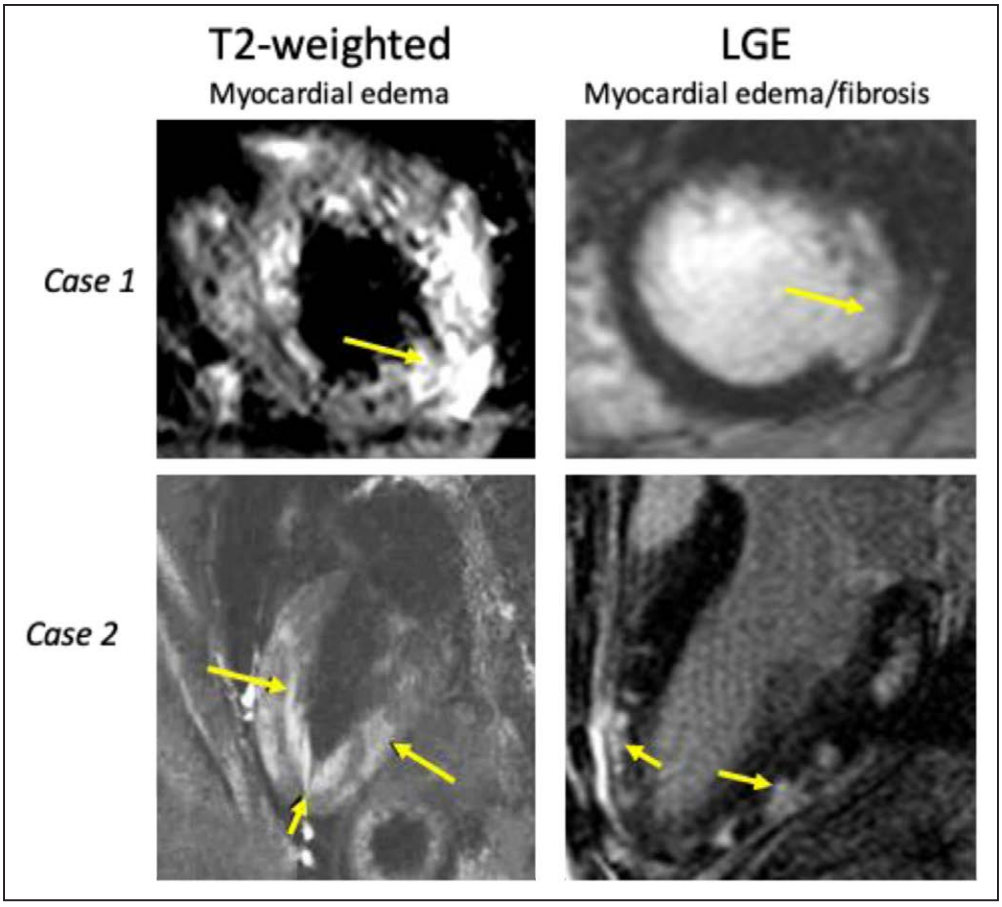

Figure 1. T2-weighted (edema) and late gadolinium enhancement (LGE) imaging in 2 cases of acute myocarditis.
In case 1, significant myocardial edema spans the inferior and lateral left ventricle (areas of brightness on T2-weighted imaging, yellow arrows), which corresponds to areas of LGE. In case 2, there are patchy areas of T2 brightness, signifying edema, with smaller areas of LGE. Images courtesy of Dr Raymond Kwong (Brigham and Women's Hospital).

taking into account at least 2 of 3 CMR tissue characterization criteria for myocarditis (79% diagnostic accuracy[29]): (1) edema (as quantified by global or regional T2 enhancement), (2) scar or active inflammation (by LGE imaging, usually in a regional or global subepicardial distribution, although subendocardial infarct LGE has been observed[29–31]; Figure 1), or (3) evidence of myocardial hyperemia (by enhancement early after gadolinium).[27,32] The sensitivity may change with clinical severity, with the greatest sensitivity in more severe presentations (eg, infarct-like presentation versus heart failure or arrhythmia[30]; elevated cTn level on admission[33]).

In small studies, the location of LGE may suggest a specific viral pathogen (lateral wall LGE with parvovirus B19; septal LGE with human herpesvirus-6[34]). Although not specific, some authors suggest that more extensive LGE across different areas of the myocardium may raise suspicion for GCM.[35] With respect to eosinophilic myocarditis, global myocardial edema (by T2-weighted imaging) may be an early feature, inversely proportional to cardiac function, and may resolve over time.[36,37] Diffuse (potentially subendocardial) LGE and midwall LGE may also be present,[38] with resolution over time as well.[39] In general, although CMR may not be considered early in the diagnostic algorithm of FM because of patient instability (>10 days later than in non-FM), patients with FM more often display diffuse LGE relative to patients without FM[21] (Figure 2).

In recognition that LGE and T2 imaging may not capture diffuse inflammatory and fibrotic myocardial insults with sufficient sensitivity, modern approaches to map diffuse myocardial fibrosis, inflammation, or injury even at a subclinical level (eg, extracellular volume fraction mapping and T1/T2 mapping) have emerged as diagnostic adjuncts. These techniques allow quantification of CMR relaxation parameters along a continuum with precision, reflecting the degree of inflammation or fibrosis occurring below the thresholds of traditional LGE or T1/T2–weighted imaging. Indeed, the addition of tissue mapping (extracellular volume fraction or T1 mapping) yielded significant improvement in diagnostic accuracy over traditional Lake Louise criteria.[40–42] Even noncontrast CMR measurements of native T1 or T2 may augment diagnosis[43–46] and track myocarditis disease activity and therapeutic

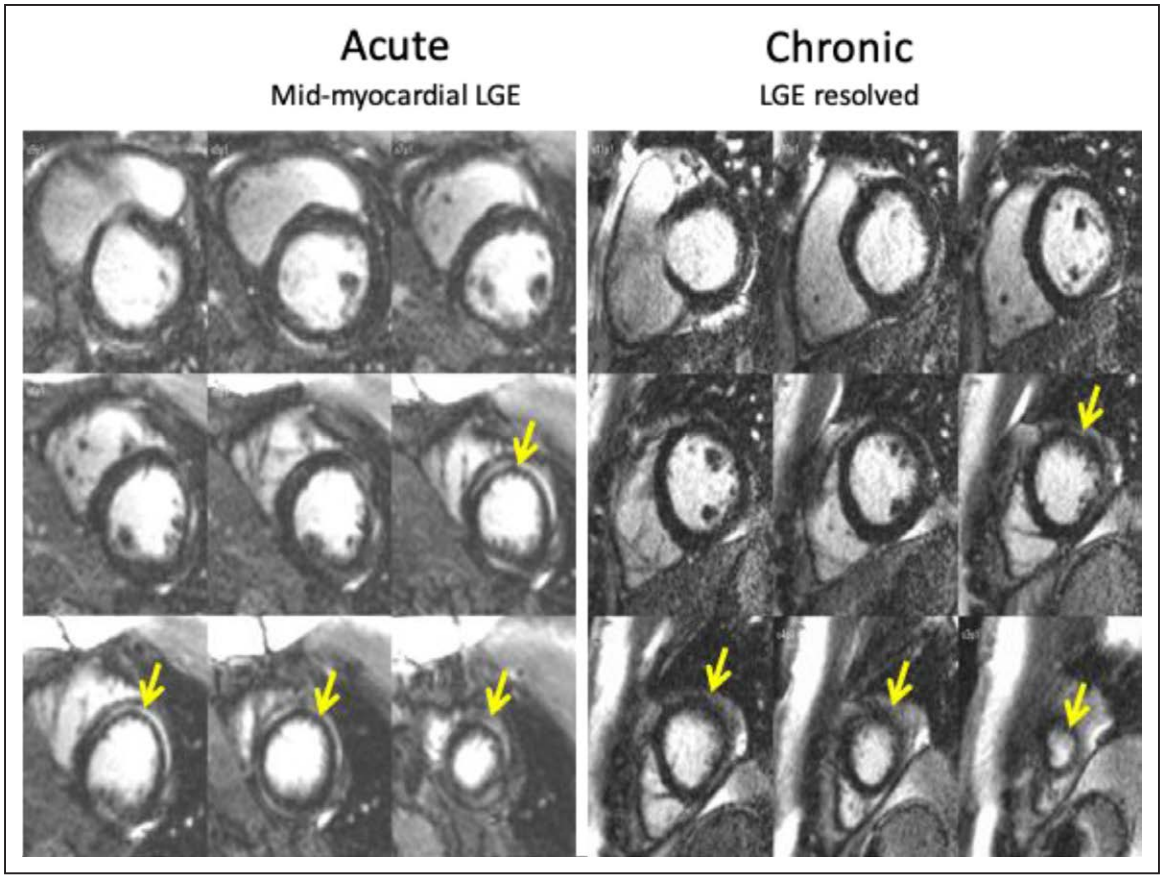

Figure 2. Late gadolinium enhancement (LGE) images in the acute and chronic setting of suspected acute myocarditis.
LGE seen in the acute (left) setting, mid-myocardial, is often present in the acute phase and resolved at follow-up. These areas may initially represent acute myocardial edema (yellow arrows) and resolve over time (right). Images courtesy of Dr. Raymond Kwong (Brigham and Women's Hospital).

response.[47–50] Given burgeoning evidence of CMR tissue mapping in myocarditis, society guidelines have now begun to suggest consideration of these mapping techniques in diagnosis.[51]

Cardiac Computed Tomography

Contrast-enhanced cardiac computed tomography (CT) has generally been used to evaluate coronary artery disease as a cause of myocardial dysfunction. Nevertheless, several reports suggest that findings similar to LGE on CMR can be observed with delayed CT imaging after contrast administration[52–60] in a fashion comparable to CMR,[61,62] and newer techniques (eg, extracellular volume fraction mapping[63]) may emerge soon as adjunct diagnostic biomarkers. Although CT may have improved resolution relative to CMR imaging, the need for contrast administration (especially after recent coronary angiography that many patients undergo) and ionizing radiation is an important limitation.[64]

Nuclear Imaging

Several nuclear imaging modes have been used to detect myocarditis, among them gallium-67 imaging,[65] technetium-99m-MIBI or thallium-201 single-photon emission CT imaging,[65] indium-111 anti-myosin antibody imaging,[66–69] and 18-flouro-deoxyglucose positron emission tomography.[70] Of note, perfusion defects on technetium-99m-MIBI or thallium-201 single-photon emission CT imaging are less specific to myocarditis, although perfusion defects without epicardial coronary artery obstruction prompt consideration of myocarditis.[71] Before the widespread application of CMR, anti-myosin imaging had a long-standing role in diagnosis of myocarditis, as well as potential prognostic implications (eg, in children[72]). Nevertheless, several key limitations (including imaging time, radiation, and accessibility[64]) and the availability of CMR have curtailed its clinical use. Alternatively, positron emission tomography has emerged as a potential novel mode to detect myocardial metabolism and inflammation in a fashion complementary to CMR.[73] Although studies in positron emission tomography have focused on sarcoid, positron emission tomography imaging early in the course of myocarditis may detect active metabolism/inflammation,[70] and newer imaging techniques targeting inflammatory cells (eg, somatostatin receptor imaging[74]) and imaging of molecular pathophenotypes relevant to myocarditis (inflammation, apoptosis, fibrosis[75]) are emerging.

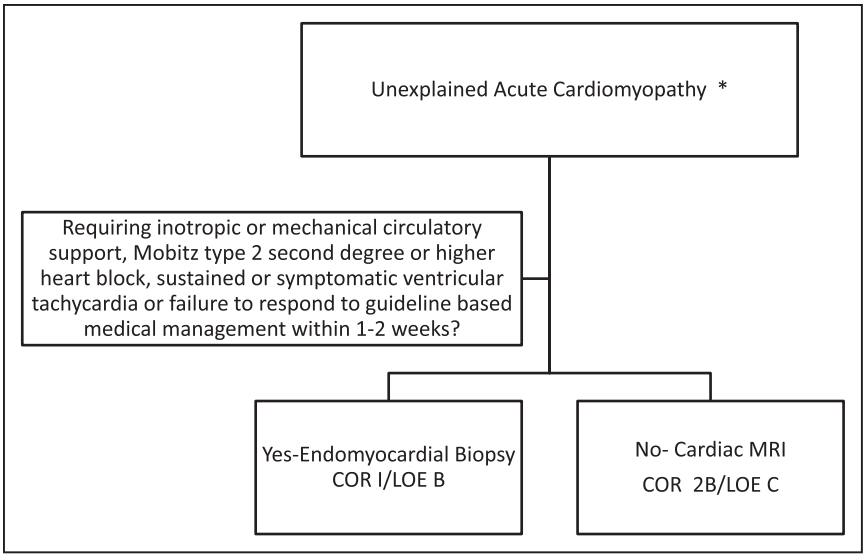

Figure 3. Indications for endomyocardial biopsy (EMB).
Guideline-based algorithm for whether EMB is indicated. COR indicates Class of Recommendation; LOE, Level of Evidence; and MRI, magnetic resonance imaging. *Usually a dilated cardiomyopathy. Fulminant myocarditis may have normal end-diastolic diameter with mildly thickened walls. Exclude ischemic, hemodynamic (valvular, hypertensive), metabolic, and toxic causes of cardiomyopathy as indicated clinically. Reprinted from Bozkurt et al.[3] Copyright © 2016, American Heart Association, Inc.

EMB, CORONARY ANGIOGRAPHY, AND INVASIVE HEMODYNAMICS

In the setting of cardiogenic shock, right-sided heart catheterization and coronary angiography are essential to guide management strategies. The decision to perform an EMB at the time of right- and left-sided heart catheterization is more nuanced and depends on clinical suspicion for myocarditis, operator experience, and pretreatment with anticoagulants, antiplatelet agents, and lytic therapy. According to a joint statement from the AHA, American College of Cardiology, and ESC in 2007, there are 2 situations in which EMB should be performed (Class I indication). The first is unexplained, new-onset heart failure of <2 weeks' duration that is associated with hemodynamic compromise, and the second is in the setting of unexplained new-onset heart failure between 2 weeks' and 3 months' duration that is associated with a dilated LV and new bradyarrhythmia (Mobitz II or complete heart block), new ventricular arrhythmias, or a failure to respond to standard care within 1 to 2 weeks of diagnosis.[76]

In 2013, the ESC Working Group on Myocardial and Pericardial Disease recommended that coronary angiography and EMB should be considered in all patients with clinically suspected myocarditis.[77] In 2016 an AHA scientific statement confirmed and expanded the 2007 joint statement from the AHA, American College of Cardiology, and ESC, stating that EMB may be considered in heart failure that is rapidly progressing when there is a high suspicion that the cause can be confirmed only by myocardial histology. Moreover, it assumes that therapy is available and effective for this diagnosis.[3] EMB is limited by sampling error, which can be improved by using imaging to direct the site of the biopsy. Some clinicians recommend screening CMR imaging for evidence of myocardial edema, infiltration, or scarring and proceeding to EMB only if the magnetic resonance imaging is abnormal; LGE may persist despite normalization of cardiac enzymes and biomarkers.[78] EMB can be considered the primary diagnostic strategy[76,79] when magnetic resonance imaging is not possible (eg, shock, presence of metal devices) if experienced operators and cardiac pathologists are readily available. According to guidelines, however, indications for EMB would be present for most patients presenting with FM and are given in Figure 3.[3] Further precision may be achieved by the use of viral genome analysis, immunohistology, or transcriptomic biomarkers when diagnostic uncertainty exists despite histology.[80]

EARLY INITIAL MANAGEMENT AND STABILIZATION AMONG PATIENTS WITH FM

Among patients with FM, the initial presentation is often one of cardiogenic shock. The recognition and management of this syndrome with vasoactive drugs and mechanical support have been reviewed extensively in other comprehensive reviews and scientific statements, including the recent document published in *Circulation*, "Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association."[81–86] Figure 4 illustrates the general approach to the initial support of patients in cardiogenic shock. Cardiogenic shock in FM is often accompanied by arrhythmias, including atrial and ventricular tachyarrhythmias, bradyarrhythmia caused by heart block, syncope, and sudden cardiac death.[87] Eighteen percent of patients with suspected myocarditis in the European Study of Epidemiology and Treatment of Inflammatory Heart Disease had an arrhythmia.[4] Bradyarrhythmias are less common than tachyarrhythmias unless the myocarditis is caused by sarcoidosis, Chagas disease, or a systemic autoimmune disease.[88] Exercise can trigger these arrhythmias; thus, the current AHA scientific statement

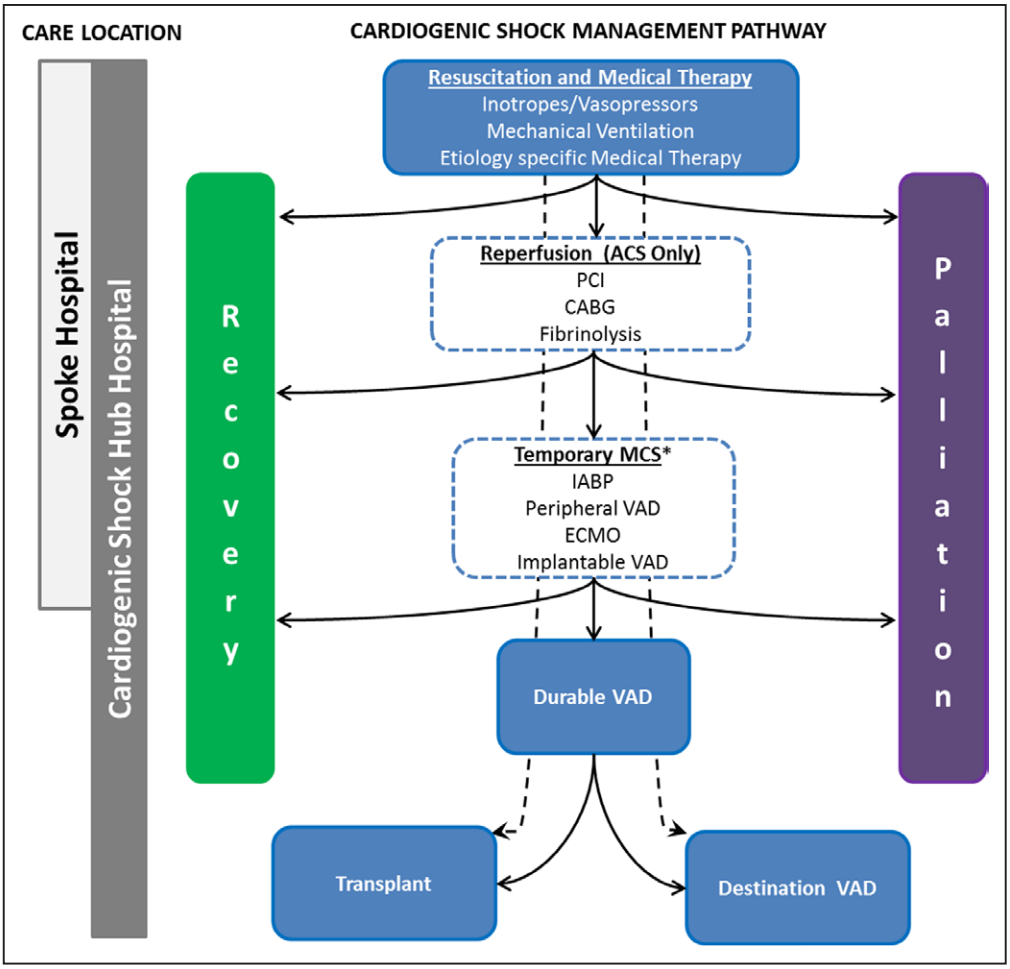

Figure 4. General approach to initial stabilization of patients in cardiogenic shock.
ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting procedure; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; and VAD, ventricular assist device. Reprinted from van Diepen et al.[86]

and ESC position statement[15] recommend that patients with acute myocarditis do not participate in competitive sports in the setting of ongoing inflammation. Arrhythmias in these patients can be the result of edema or scar, and most studies suggest that patients with LGE on CMR are more likely to have ventricular arrhythmias.[89–91]

Patients may present in an unstable condition, brought in by emergency medical services from home or in transfer from another facility. For patients who are in cardiac arrest or a pulseless arrhythmia, initial management follows the current AHA guidelines for advanced cardiac life support, beginning with a focus on circulation, airway, and breathing. Guidelines recently have consistently focused on high-quality chest compressions.[83] In the emergency department setting, management is geared toward resuscitation and stabilization as a definitive diagnosis is simultaneously explored. For institutions without advanced heart failure surgical and medical management capabilities, including expertise in myocarditis management, consideration for transfer from the emergency department directly to a tertiary referral hospital is warranted. Initial stabilization requires hemodynamic and, if needed, respiratory support to maintain adequate tissue perfusion and end-organ oxygen delivery. Thus, sufficient stabilization, including mechanical circulatory support (MCS) devices or extracorporeal life support (ECLS), may be needed. Initial ancillary testing in the emergency department is summarized in Table 2. Testing should include a venous blood gas for pH, lactate (which can be run rapidly and offers a snapshot of the patient's perfusion and ventilation status), complete blood count, and basic metabolic panel, as well as total and fractionated bilirubin, alanine transaminase, and aspartate transaminase, for early signs of right-sided heart failure. Cardiac biomarkers minimally including cTn and BNP (B-type natriuretic peptide) or NT-proBNP (N-terminal pro-BNP) should be sent to confirm the presence of increased myocardial wall stress and evidence of myonecrosis.

The emergency department staff should be aware of hospital resources and consider transfer to a tertiary facility with expertise in advanced circulatory support and transplantation if early signs of circulatory failure

Table 2. Initial Ancillary Testing in the Emergency Department for the Hemodynamically Stable Patient With Suspected Early FM

ECG: ST-T–wave changes, concave ST-segment elevation, focal ST-segment elevation mimicking an AMI in a particular coronary distribution. Diffuse ST-segment elevation with PR depression may be present, suggesting inflammation of the pericardium also.
Chest x-ray
Complete blood cell count, including differential
Basic metabolic panel
CPK, CK-MB, cTn
Natriuretic peptide
ABG or VBG, lactate
LFTs
Blood cultures (for febrile patients)

ABG indicates arterial blood gas; AMI, acute myocardial infarction; CK-MB, creatine kinase-mF; CPK, creatine phosphokinase; cTn, cardiac troponin; FM, fulminant myocarditis; LFT, liver function test; and VBG, venous blood gas.

Table 3. Initial Management Considerations in FM

Because patients with myocarditis are often young and have no known cardiac disease, hypotensive patients are often given intravenous fluids, which can cause worsening of symptoms and hemodynamics in the setting of an acute heart failure syndrome or cardiogenic shock.
Vasopressor therapy with norepinephrine has been associated with fewer arrhythmias than dopamine among a cohort of patients with AMI shock.[96] Whether this is generalizable to patients with FM is unknown.
Among patients with cardiogenic shock related to an AMI, norepinephrine had improved survival compared with dopamine.[96] Norepinephrine may be used preferentially as the vasopressor to support blood pressure in patients with combined shock and systemic inflammation such as AMI. This may extrapolate to FM, but the hypothesis has not been rigorously tested.[86]
Early invasive management, particularly to rule out epicardial coronary disease and to measure hemodynamics to guide the best support modalities, and often EMB if indicated may reduce the time of end-organ and brain hypoperfusion and decrease time to the specific diagnosis of the cause of FM that may have a specific treatment.[86,97]

AMI indicates acute myocardial infarction; EMB, endomyocardial biopsy; FM, fulminant myocarditis; LFT, liver function test; and VBG, venous blood gas.

are present. Among institutions with a multidisciplinary shock team, that team should be activated to leverage multiple disciplines to determine the most appropriate modality of support and to implement the plan rapidly, before multisystem organ failure begins or worsens. If available, an ECLS team from a tertiary care center may be dispatched for evaluation, possible ECLS cannulation, and retrieval of patients who are too unstable for transfer.[86]

Often, ECLS is the quickest way to fully support an unstable patient's circulation and oxygenation/ventilation, if necessary, without the risk of inotrope-induced arrhythmias among patients already at risk.[81] By definition, nearly all patients with FM will require vasoactive drug support or temporary MCS to bridge them to a stage at which their own circulation or a more durable solution can take over support of their end-organ function. Many centers have experience with percutaneous insertion of ECLS cannulas at the bedside and immediate initiation of support. Centers are becoming increasingly adept at using percutaneous biventricular assist devices in patients without the need for extracorporeal oxygenation, eliminating some of the risks associated with ECLS and the inherent need for an oxygenator. Moreover, these percutaneous assist devices provide biventricular unloading, thereby decreasing myocardial wall stress and reducing the likelihood of exacerbating injury to the already inflamed heart. Although FM is too rare to have randomized controlled trials evaluating the use of temporary MCS devices to support the failing circulation, several case reports have described recovery once the circulation was fully supported and the patient's end organs perfused, allowing time for the heart to recover.[92,93] In patients with fulminant lymphocytic myocarditis, the heart will often recover spontaneously with time, and in other immune-mediated FM subtypes, as described later, the heart can recover with the appropriate immunomodulatory therapy.[94,95] In the absence of recovery, temporary MCS can offer short-term stability and support of the patient's other organs while the patient awaits cardiac transplantation. A partial list of specific management considerations among patients presenting with suspected FM is given in Table 3.

Once properly stabilized, regardless of pathogenesis, all patients with FM and contractile dysfunction benefit from evidence-based neurohormonal antagonist therapy. Heart failure therapy with neurohormonal antagonists and diuretics is the cornerstone of management.

Specific Conditions That May Result in FM

Lymphocytic Myocarditis

Lymphocytic myocarditis is a clinicopathological disorder defined by the presence of a mononuclear cellular infiltrate and LV dysfunction. It is an inflammatory disease of the heart, and criteria have been established that incorporate histological and immunohistochemical findings. It should be distinguished from other inflammatory disorders of the heart by the nature of other possible cellular infiltrates, for example, eosinophils, neutrophils, and macrophages. It can clinically present in subclinical, subacute, acute, and fulminant forms, and the trajectory of patients is highly variable, regardless of presentation.[87,98,99] Prompt diagnosis is critical for management because the prognosis and likelihood of recovery are better with lymphocytic myocarditis than with nonspecific histological findings or GCM.

Estimates of incidence vary widely because of the inherent biases in epidemiological reporting and challenges in establishing the diagnosis; published estimates likely underestimate the commonality. According to data from the *International Classification of Diseases*,

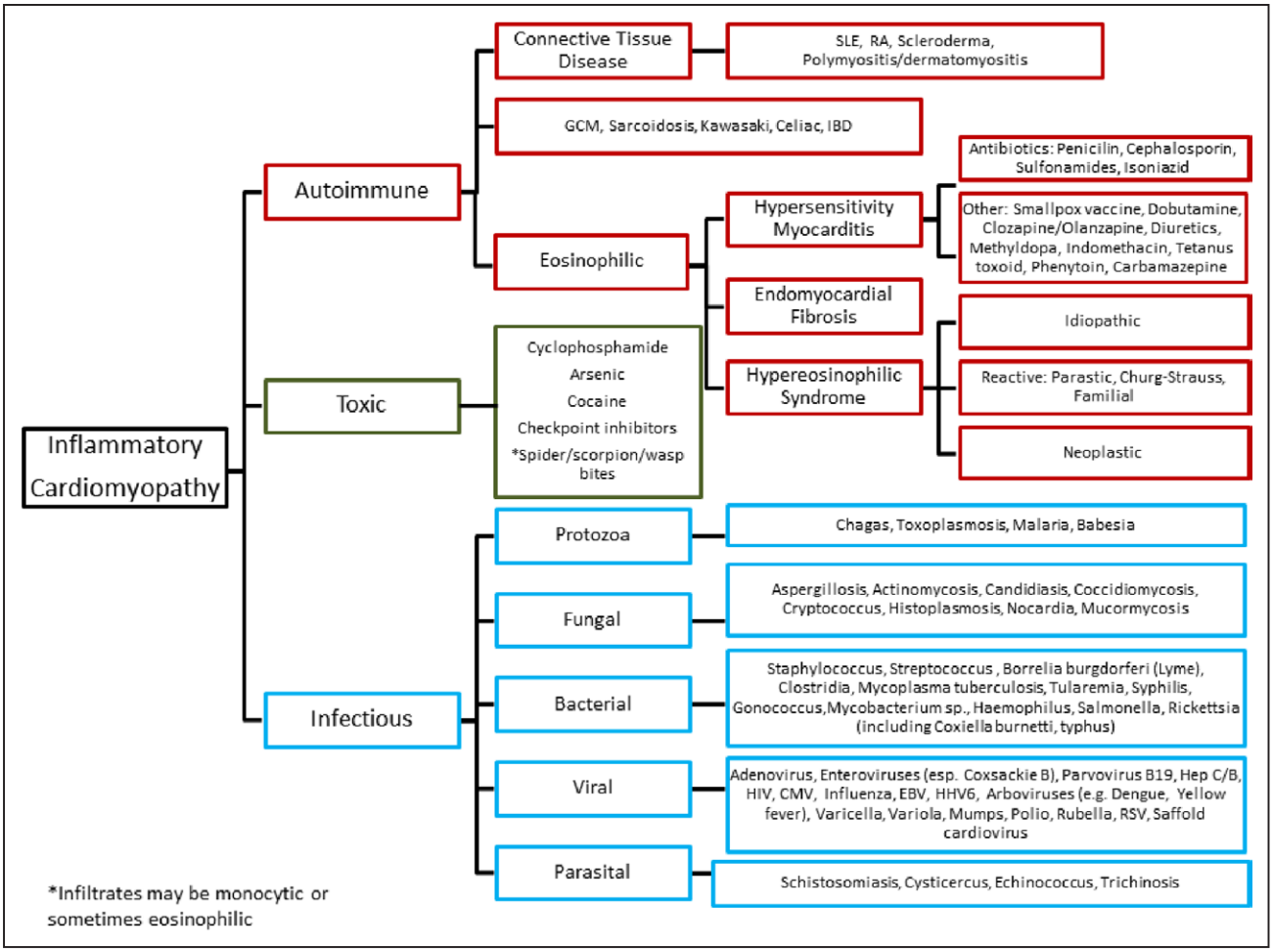

Figure 5. Causes of lymphocytic myocarditis.
Diagram demonstrating the primary causes and associated subcategories of lymphocytic myocarditis. GCM indicates giant cell myocarditis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; and SLE, *systemic lupus* erythematosus. Reprinted from Trachtenberg and Hare.[99] Copyright © 2017, American Heart Association, Inc.

the annual prevalence worldwide was ≈22 cases per 100 000 patients.[100] In a study of >500 000 military male recruits, 98 cases were documented.[101] As many as 5% of patients who have objective evidence for an acute viral infection may have some form of myocarditis.[98,102] In an autopsy series from Japan, nonspecific myocarditis was reported in 0.11%.[103] Asymptomatic elevations in cTn are not uncommon in vaccination programs[104]; myocarditis, with or without pericarditis, in smallpox vaccination programs has been reported to be 5 to 6 per 10 000 vaccines.[105] In retrospective series of patients who present with dilated cardiomyopathy, myocarditis was implicated in 9% to 10%.[8] Viral infection, defined as a detectable viral genome by reverse transcription–polymerase chain reaction or polymerase chain reaction, is likely the most common cause of lymphocytic myocarditis and can be found in 30% to 40% of cases (Figure 5).[87,98,99] Viral association with myocarditis may include direct myocardial infection or a cross-reactive immunological reaction as a result of the virus, so-called molecular mimicry.

Clinical presentations vary widely and may include more nonspecific (eg, shortness of breath) to more dramatic (eg, sudden death) presentation observed in all myocarditis subtypes. (The Appendix provides further details on the microbiology and immunology of lymphocytic myocarditis.)

Treatment of lymphocytic myocarditis has been focused primarily on the myocardial consequences of the inflammatory injury. Various reports and case series have described the spontaneous recovery of LV dysfunction while the patient is supported on MCS.[106,107]; overall survival is improved if end-organ function is simultaneously maintained with pharmacological support or MCS. A number of cytokines can depress myocardial function in experimental models, and these may have a role in the pathogenesis of acute myocardial pump failure in human myocarditis. However, anti–tumor necrosis factor treatments did not improve outcome in acute cardiomyopathy. The role of specific anti-inflammatory agents targeting interleukin-17 and interleukin-1 is under investigation. Heart transplantation can be successful for

Table 4. Selected Trials of Treatment in Lymphocytic Myocarditis

Therapy	Study	n	Biopsy?	Placebo	Between-Group Differences	Notes
Prednisone	Parrillo et al,[109] 1989	102	Yes	No	None in LVEF	Benefit in inflammation on biopsies
Prednisone	Latham et al,[110] 1989	52	Yes	No	None in survival	Only 13% of patients with myocarditis
Prednisone+AZA/CyA,	Mason et al,[111] 1995	111	Yes	Yes	None in LVEF	All enrolled patients with myocarditis
Prednisone+AZA	Wojnicz et al,[112] 2001	84	Yes	Yes	Change in LVEF better	Biopsy evidence for HLA expression
Prednisone+AZA	Frustaci et al,[113] 2009	85	Yes	Yes	Change in LVEF better	Virus negative required
IVIG	McNamara et al,[114] 2001	62	Yes	Yes	None in LVEF	Only 16% with myocarditis
IVIG+ IA	Staudt et al,[115] 2001	25	Yes	No	Change in LVEF better	Improved NYHA class
IVIG	Kishimoto et al,[116] 2014	41	Yes	No	Survival benefit	No difference between groups in LVEF
IFN-α	Miric et al,[117] 1996	38	Yes	No	Change in LVEF better	Some patients received thymomodulin
Ongoing trials						
Prednisone+AZA	NCT01877746*	234	Yes	No	Change in LVEF at 12 mo	Virus negative required
IVIG	NCT00892112*	50	Yes	Yes	Change in LVEF at 6 mo	Evidence for parvovirus
Anakinra	NCT03018834*	120	No	Yes	Days alive free of HF complications	Diagnosis by chest pain, Tn, CMR

AZA indicates azathioprine; CMR, cardiac magnetic resonance; CyA, cyclosporine A; HF, heart failure; HLA, human leukocyte antigen; IA, intra-arterial; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and Tn, troponin.

*ClinicalTrials.gov unique identifier.

fulminant lymphocytic myocarditis, although it is uncommon.[108]

Few prospective blinded randomized trials have specifically targeted viral infections or the associated inflammatory cascades in lymphocytic myocarditis (Table 4). Antiviral approaches have been extensively assessed in vitro, but few human studies have been reported. Interferons have been used as an antiviral strategy; in 22 patients with LV dysfunction and enteroviral or adenoviral infection, interferon-β led to clearance of the virus and improvement in ventricular function in 15 patients.[118] In a study of 143 patients with heart failure symptoms and biopsy evidence of specific viral genomes, treatment with interferon-β1b for 24 weeks was associated with more effective viral clearance and improvements in patient symptoms and quality of life compared with placebo and was well tolerated.[119] Most studies of immunomodulation or antiviral strategies have included mostly patients with a more chronic disease course, as opposed to the fulminant variety.

Single-center experiences and case reports of various immunomodulatory therapies have been difficult to interpret because many patients will recover spontaneously with general heart failure management. For example, in the Myocarditis Treatment Trial,[111] the use of cyclosporine and steroids was associated with an improvement in LVEF, but the improvement was not statistically different from that of the placebo-treated patients, and no difference in mortality was seen. Trials to date have also been limited in sample size (eg, no trial >200 patients), duration of follow-up (most <1 year), and end points (often LVEF). Enrollment of appropriate patients has also been difficult. For instance, in the Myocarditis Treatment Trial, >2000 patients were screened in order to randomize 111 patients.[111]

Corticosteroids are commonly given in clinical practice, in large part because of clinician comfort and experience with this agent. However, in the only 2 randomized prospective controlled trials, no clinically relevant benefit was seen.[109,110] Combining corticosteroids with other agents may be more effective; in 2 randomized controlled trials with azathioprine and prednisone,[112,113] improvements in LVEF and patient symptoms were observed in subjects with symptoms for >6 months. In contrast, the use of cyclosporine and azathioprine with prednisone failed to improve LVEF and patient outcomes relative to placebo.[111] In cases of fulminant disease and cardiogenic shock, corticosteroids are also often used despite lack of clear evidence of benefit[15] and an undefined risk of adverse effects.

Intravenous immunoglobulin (at a dose of 0.5 g/kg) is commonly used in pediatric lymphocytic myocarditis,[120] but the controlled experience in adults is limited. Intravenous immunoglobulin has been associated with improvement in LVEF when combined with immunoadsorption[115] but no improvement when used alone.[114,116]

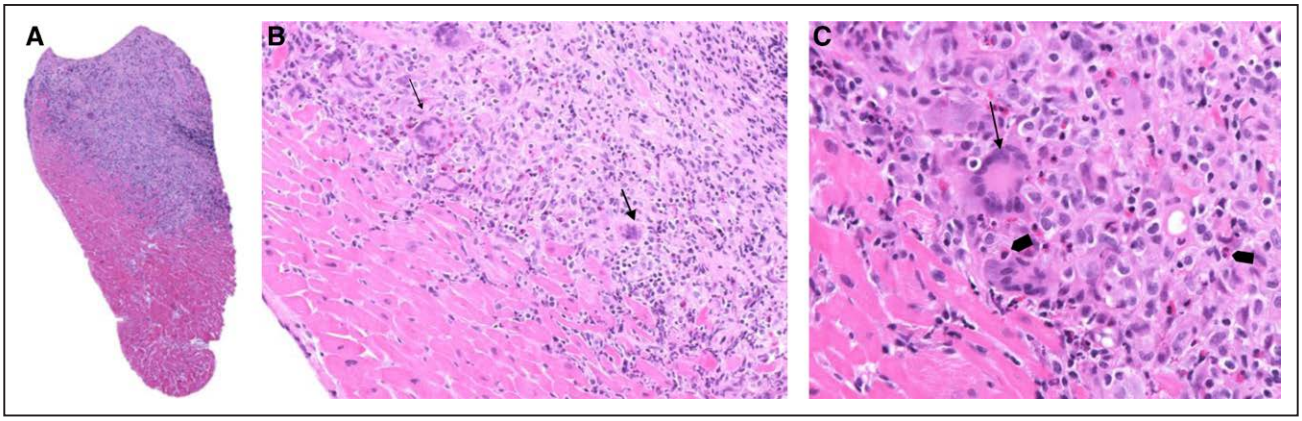

Figure 6. Giant cell myocarditis histology at endomyocardial biopsy (hematoxylin and eosin [H&E] stains).
H&E–stained slides in (**A**) low-power, (**B**) medium-power, and (**C**) high-power microscopy demonstrating myocytolosis and dense mixed inflammatory infiltrate composed of scattered multinucleated giant cells, frequent eosinophils, and mononuclear inflammatory cells with necrotic myocardium. Arrows in (**B**) and (**C**) indicate multinucleated giant cells. Arrowheads indicate eosinophils. Images kindly provided by Chrystalle Katte Carreon, MD.

Statin therapy may also have benefits. In a small randomized experience with atorvastatin, patients' LVEF and New York Heart Association class improved relative to those of control subjects over 6 months of treatment.[121] A recent systematic review and meta-analysis of controlled randomized trials of immunotherapy for myocarditis[122] concluded that no overall benefit in LVEF was seen in 612 patients who had biopsy-proven myocarditis and an LVEF <45%. Combination therapy may have benefit over single-agent immunomodulatory therapy, but properly powered trials have yet to be performed. Benefit may depend on the clearance of virus.[113,123,124]

Giant Cell Myocarditis

GCM is an uncommon and frequently fatal form of FM that affects primarily young and middle-aged adults.[87] The most common presentation is acute heart failure complicated by ventricular arrhythmias and progressive hemodynamic deterioration. Up to 25% of patients with GCM have a history of other autoimmune disorders.[125] In both experimental models and clinical studies, GCM responds to cyclosporine-based immunosuppressive therapy, suggesting that most cases are autoimmune rather than the result of an active infection. Without immunosuppressive therapy and guideline-directed medical management of circulatory failure, the most frequent outcome is death or transplantation within the first year after diagnosis. After transplantation, GCM recurs in 20% to 25% of allografts.[126,127]

Delay in diagnosis is the major error in management. Patients with typical features suggestive of GCM, for example, fulminant heart failure with ventricular arrhythmias and lack of response to guideline-directed medical management, should have an EMB.[3,76,128] Anecdotal reports with CMR imaging suggest diffuse abnormalities in T1 and T2 mapping and images, but patients with GCM often are too unstable for CMR imaging.[28,35] Uncertainty about the histological diagnosis is the second major pitfall in management. Because of sampling error, repeat EMBs, including the LV, are sometimes needed to diagnose GCM.[129] Because the characteristic giant cells appear after 1 to 2 weeks, the biopsy samples obtained in the first days of the illness may resemble a necrotizing eosinophilic myocarditis (NEM) without giant cells. GCM may resemble cardiac sarcoidosis but does not have the noncaseating granulomas or much fibrosis. The degree of eosinophil infiltrate varies but is usually more than in cardiac sarcoidosis.[130]

The pathological criteria for GCM are a diffuse or multifocal inflammatory infiltrate consisting of lymphocytes with multinucleated giant cells associated with myocyte damage. The giant cells are usually at the edges of the inflammatory lesions and are frequently associated with intact and degranulated eosinophils (Figure 6).

Occasionally, GCM will present as idiopathic complete heart block. In a study from Finland, 25% of individuals <55 years of age with clinically idiopathic heart block had GCM or cardiac sarcoidosis on heart biopsy.[131] In this setting, the prognosis is guarded with a 39% rate of cardiac death, cardiac transplantation, ventricular fibrillation, or treated sustained ventricular tachycardia over 48 months. GCM can also have a period of stability after presentation, lasting for a year or more, after which the clinical course may be progressive.[132] In contrast, isolated atrial GCM that presents with atrial rather than ventricular arrhythmias in the absence of heart failure has a good prognosis.[133]

In addition to guideline-directed medical management, select immunosuppressive regimens as detailed below may improve transplantation-free survival in biopsy-proven, acute GCM when administered within the first 12 weeks after symptom onset. The only experimental model of GCM occurs in the Lewis rat after immunization with cardiac myosin in a complete Freud adjuvant.[134] In this model, inflammation decreases and

survival increases with calcineurin inhibitor or anti–T-cell antibody therapy but not with corticosteroids.[135,136] In a multicenter registry report, a similar pattern of improved transplantation-free survival was observed after immunosuppressive therapy for acute GCM that included cyclosporine.[2] These data were confirmed in a prospective trial, a contemporary observational registry, and multiple case reports.[10,94,137] Antithymocyte globulin has been used successfully in native heart GCM,[138] and an anti-CD52 monoclonal antibody has been used in allograft GCM.[139]

MCS can and should be used as a bridge to transplantation or recovery in GCM,[140] sometimes with cytolytic immunosuppression.[93] Shorter-term MCS devices may provide a bridge to recovery or a more durable device.[141,142] Despite higher rates of early rejection, posttransplantation survival of patients with GCM is similar to that of patients with other cardiomyopathies.[143]

Treatment of GCM, depending on the stage of progression, may require rapid initiation of biventricular MCS[144] as a lifesaving measure to stabilize the patient's end-organ function and to maintain hemodynamic stability in the catheterization laboratory during coronary angiography, hemodynamic determination with pulmonary artery catheterization, and EMB. MCS has the additional benefit of providing biventricular support if an EMB were to irritate the ventricle, leading to persistent ventricular tachycardia or ventricular fibrillation. At the time of heart catheterization, angiography, and possible biopsy, strong consideration should be given to inserting biventricular mechanical support if hemodynamic data indicate severe biventricular failure. Other indications for early biventricular support are persistent unstable ventricular arrhythmias or high-grade intranodal block. Extracorporeal life support is another well-founded treatment option because it can be inserted rapidly by well-trained surgeons or interventional cardiologists in the operating room, peripherally in the cardiac catheterization laboratory under fluoroscopic guidance, or emergently at the bedside. Before the existence of reliable MCS devices in the 1980s and the use of orthotopic heart transplantation among patients with GCM, GCM was almost exclusively a diagnosis made at postmortem autopsy.[2,145] Unlike its phenotypic cousin, fulminant lymphocytic myocarditis, GCM rarely resulted in spontaneous recovery after a period of mechanical support.[94,146] This emphasizes the importance in making a tissue diagnosis; the 2 forms of FM often present in a similar fashion although they have widely varied prognoses.[146]

If a high suspicion for immune-mediated FM exists, 1 g solumedrol is often administered urgently, before biopsy-confirmed diagnosis or further diagnostic testing. Steroids will not obscure the results of the biopsy if given before this diagnostic test. If the diagnosis is GCM, other immunosuppressing agents will need to be added to obtain effective treatment. Whether steroids are helpful in fulminant lymphocytic myocarditis (or acute lymphocytic myocarditis) is unclear. Overall, the 2016 AHA scientific statement on current diagnostic and treatment strategies for specific cardiomyopathies does not generally recommend empirical, upfront, immunomodulatory agents before diagnosis for myocarditis.[3]

As mentioned, in the absence of established medical treatment, GCM was not survivable before the advent of MCS as a bridge to transplantation and the advances made in orthotopic heart transplantation management. As the understanding of the basic pathophysiology and natural history of GCM increased, medical treatment targeted suppressing the immune system.

One way to conceptualize GCM, especially because it tends to comigrate with other autoimmune diseases such as autoimmune thyroiditis,[147,148] is of an autoimmune disease similar in presentation to high-grade cellular rejection of a solid-organ transplant, in particular of the heart. A prospective registry of patients with GCM demonstrated that monotherapy with immunosuppression using corticosteroids alone (versus no steroids) was not statistically significantly associated with prolonging transplantation-free survival.[2] A combination of corticosteroid therapy and other immunosuppressive therapies appeared to prolong transplantation-free survival but was not curative.[2,94] In particular, case reports demonstrated that 1 patient who abruptly discontinued immunosuppression died of recurrent GCM.[94]

Early immunosuppressant therapy, particularly combination regimens that include steroids and other agents such as cyclosporine, azathioprine, or muromonab-CD3, was shown to extend the median transplantation-free survival from 3.0 to 12.4 months.[2] In the Multicenter-GCM Treatment Trial, 11 participants were treated with corticosteroids and cyclosporine, and most also received muromonab-CD3. The 1-year transplantation-free survival was 73% (8 of 11 patients), confirming earlier data with combination immunosuppression.[94] Adverse effects of muromonab-CD3 such as cytokine release syndrome have limited contemporary use of this medication in favor of the less toxic antithymocyte globulin, and triple immunosuppression with corticosteroids, cyclosporine (with a target blood level of 150–300 ng/mL), and azathioprine or mycophenolate mofetil is being used more frequently.[129,149]

In a case series out of Finland, 70% of 37 patients were treated with triple immunosuppression, with 1- and 5-year transplantation-free survival rates of 80% (95% CI, 64–90) and 58% (95% CI, 44–70).[150] Given that these initial regimens were used when cyclosporine and azathioprine were considered standard of care for preventing cellular rejection after orthotopic heart transplantation, treatment for GCM mirrored these regimens with documented success; thus, clinicians were appropriately cautious about deviating from these published protocols. More recently, the solid-organ transplantation literature

demonstrated decreased adverse effects and increased efficacy with tacrolimus/mycophenolate–based regimens relative to cyclosporine/azathioprine–based regimens. Thus, centers have begun to preferentially use tacrolimus and mycophenolate in a protocolized fashion with successful outcomes. A few published case reports on the use of tacrolimus (with a target blood level between 8 and 12 ng/mL for short-term therapy and 6 and 8 ng/mL for long-term therapy) support these newer immunosuppressants with potentially fewer side effects.[93,151,152]

There are limited data to guide immunosuppression medication doses and optimal duration of therapy in the setting of GCM for long-term maintenance of remission. Pulse steroid therapy with 1 g methylprednisolone for at least 3 days followed by oral prednisone 60 mg daily and a 10–mg/wk taper, down to a 5- to 7.5-mg daily maintenance dose, has been reported, although taper schedules vary.[94,151] Reports of patients being tapered slowly off corticosteroids (while still being maintained on low-dose calcineurin inhibitor and mycophenolate mofetil or azathioprine) exist.[129] Some patients have been tapered down to low-dose calcineurin inhibitor as a long-term treatment protocol. On the other hand, given the risk of recurrence after orthotopic heart transplantation, patients with GCM who have transplantations are typically maintained on lifelong low-dose corticosteroid. Ongoing low-dose immunosuppression, possibly lifelong, appears necessary. Slow taper to a steroid-sparing regimen has also been reported by the Beth Israel Deaconess Medical Center. Complete cessation of immunosuppressant therapy or an unmonitored decrease in dosing has led to recurrence of GCM and even cases of fatal disease relapse up to 8 years after initial presentation in both native and transplanted hearts.[153,154]

One should keep in mind that the differential diagnosis of GCM includes a rare, yet fulminant, presentation of cardiac sarcoidosis. Cardiac sarcoidosis is often an indolent disease. However, it rarely can present acutely with clinical, imaging, and pathologic features that mimic giant cell myocarditis. Although cardiac sarcoidosis is an infrequent cause of fulminant myocarditis, it should be considered on the differential diagnosis in patients presenting with new heart failure associated with conduction abnormalities, ventricular arrhythmias, or hemodynamics compromise. Like giant cell myocarditis, patients with cardiac sarcoidosis may benefit from pulse steroids upfront with a second immunosuppressive agent such as methotrexate or tumor necrosis factor alpha inhibitors once stabilized.[154a,154b]

Acute NEM

Acute NEM is a rare form of eosinophilic myocarditis that affects primarily adults and adolescents as young as 16 years of age. The clinical presentation is fulminant heart failure or sudden cardiac arrest with rates of death or transplantation up to 50% and an average symptom duration of 4 days.[155,156] Ventricular thrombosis and arterial emboli occur frequently, suggesting a possible role for prophylactic anticoagulation.[157]

Table 5. Drugs Associated With Acute NEM

Adalimumab[170]
Amoxicillin[171]
Carbamazepine[172]
Garcinia cambogia[152]
Allopurinol[173]
Clozapine[174]
Azathioprine[175]
Ibrutinib
Isoniazid
Hydrochlorothiazide
Spironolactone
Acetazolamide
Tetracycline
Sulfonamides
Sulfonylureas
Indomethacin
Amphotericin B

NEM indicates necrotizing eosinophilic myocarditis.

The most common presenting syndrome is new onset of biventricular heart failure with rapid hemodynamic deterioration requiring inotropes or MCS. A myocardial infarction–like syndrome with ST-segment elevation has also been described with a rapidly deteriorating clinical course.[158] In a minority of cases, a rash suggestive of drug-related skin reaction is present. A close temporal relationship to a new drug may indicate a hypersensitivity reaction. Table 5 contains a list of candidate drugs. The fibrosis that develops after acute eosinophilic inflammation often causes chronically elevated filling pressures and restrictive physiology.

The most common cause of acute NEM is drug hypersensitivity. Many culprit drugs are listed in Table 5, but this is not an exhaustive list. Moreover, multiple cases have been associated with hypereosinophilic syndrome, granulomatous polyangiitis, and other causes of systemic eosinophilia. Eosinophilic granules containing major basic protein are deposited on myocardial tissue, after degranulation from the eosinophil, promoting inflammation, myocardial necrosis, and thrombosis of the microvasculature. (Figure 7).[159]

The clinical presentation of myocarditis associated with hypereosinophilic syndrome tends to be more indolent, usually with less arrhythmia. Hypereosinophilic syndrome typically evolves over weeks, with symptoms of chest pain, breathlessness, and deteriorating cardiac function. A meta-analysis of 264 cases of eosinophilic myocarditis reported a mean age of 41 years (10% were <16 years of age), an equal number of male and

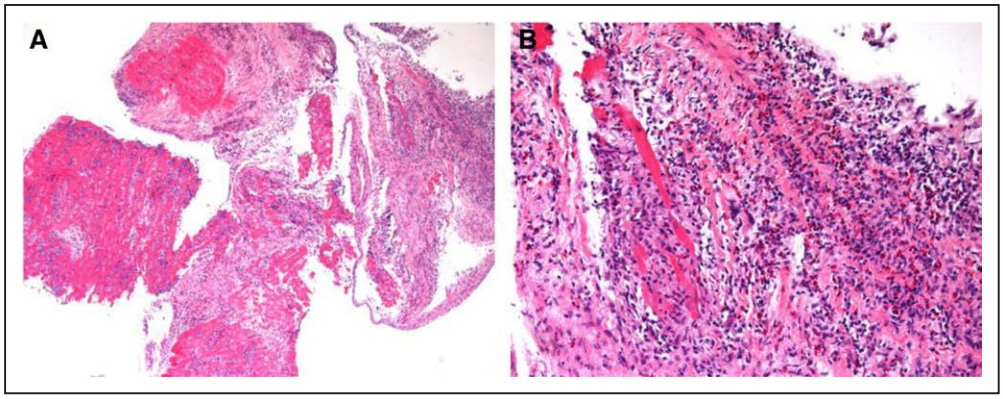

Figure 7. Necrotizing eosinophilic myocarditis.
A, Low-power (×16) view of hematoxylin and eosin (H&E)–stained myocardium demonstrating extensive hypereosiniphilic myocardium and extensive mononuclear cell infiltrate. **B**, Higher-power (×65) view of H&E–stained myocardium showing a dense inflammatory infiltrate composed of mononuclear cells, eosinophils, and macrophages. The myocardium is almost completely necrotic with evidence of microvascular thrombosis. Images kindly provided by Leslie T. Cooper, MD.

female patients, and a median LVEF at onset of 35%. Seventeen percent required inotropic support, and the in-hospital mortality was 22%.[17]

Biomarkers of myocardial damage and increased wall stress (cTn, BNP, NT-proBNP) are usually elevated. Peripheral blood eosinophilia is an important laboratory finding but may be absent.[160] The initial echocardiogram may reveal restrictive physiology with thick, edematous walls and decreased systolic function. Mural thrombosis may occur if the eosinophilic inflammation involves the endocardium. If so, Loeffler endomyocardial disease, in which restrictive physiology is the result of thrombotic obliteration of ventricular cavities, should be considered in the differential diagnosis. Mechanical causes of circulatory failure described in NEM include papillary muscle necrosis and free wall rupture.[161]

Biopsy is the gold standard for diagnosis and discloses perivascular interstitial inflammatory infiltrates with eosinophils and associated remarkable, diffuse cardiomyocyte necrosis. Necrotizing angiitis of small vessels is pathognomonic, whereas subepicardial arteries are spared. Occasional giant cells may be present, but the disease should be kept distinct from GCM. CMR can be useful for the diagnosis and monitoring of treatment response.

In contrast to GCM, NEM usually responds to high doses of corticosteroids.[162–164] Sometimes, a second agent such as mycophenolate mofetil[159] or azathioprine has been used[165] in addition to guideline-directed medical care.

Inotropic support or MCS may be needed, and a successful bridge to recovery has been described with concomitant immunosuppression.[21,92,159] The durability of recovery has been questioned because relapse with elevated cTn and impaired cardiac function has been described. If the disease relapses, therapy such as mepolizumab or campath may be considered for hypereosinophilic syndrome or drug reaction with eosinophilia and systemic symptoms–associated eosinophilic myocarditis.[166] The optimal length of steroid treatment, risk of recurrence, and anticoagulation strategy remain uncertain.

MYOCARDITIS CAUSED BY NOVEL CANCER THERAPIES

Over the past 2 decades, there has been an explosion of effective cancer therapies, resulting in an improvement in prognosis for certain cancers. However, both traditional and new cancer therapies are associated with cardiovascular toxicity, which includes myocarditis.[167] Indeed, early cardiotoxicities observed with anthracyclines included myocarditis-pericarditis syndrome.[168] More recently, however, myocarditis has become a major consideration in cardio-oncology given the advent of cancer immunotherapies.[169] Specific immunotherapies called immune checkpoint inhibitors (ICIs) have led to significant and durable responses for several cancer types. ICI are antibodies that target immune checkpoints or brakes, thus activating the immune system. As of early 2019, at least 7 ICIs were approved, with many more being tested or under development (Table 6).[176] However, ICIs can also lead to immune-related adverse events, including colitis, dermatitis, pneumonitis, endocrinopathies, and other immune-related adverse events.[177]

In 2016, Johnson et al[178] described 2 cases of fulminant and fatal myocarditis after treatment with ICI. These patients presented with refractory electrophysiological disturbances and concomitant myositis, with pathology confirming T-cell and macrophage infiltration into the myocardium.[178] Since then, other case series of myocarditis have described an estimated incidence of 0.3% to >1% when ICIs are used in combination.[179–181] The largest such case series included 101 cases of ICI-associated myocarditis; these patients had early onset of symptoms (median, 27 days after initial exposure to ICIs), frequent deaths (46% mortality), and a dramatic increase in case reports in 2017. The increase in case reports is perhaps consistent with growing recognition of this new clinical

Table 6. ICIs: FDA Approved, in Testing, or in Development

Molecular Target	Therapeutic Agent	Oncological or Testing Indication(s)
CTLA-4	Ipilimumab	Unresectable or metastatic melanoma, adjuvant for cutaneous melanoma
	Tremelimumab*	
PD-1	Nivolumab	BVAF V600 mutation-positive or wild-type unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma, classic Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of head/neck
	Pembrolizumab/lambrolizumab	Unresectable or metastatic melanoma, metastatic NSCLC, metastatic or recurrent head and neck squamous cell carcinoma
	Pidilizumab (CT-011)*	Non-Hodgkin lymphoma, melanoma, renal cell carcinoma
PD-L1	Atezolizumab	Locally advanced or metastatic urothelial carcinoma, metastatic NSCLC
	Avelumab	Merkel cell carcinoma, urothelial carcinoma
	Durvalumab	Urothelial carcinoma
	BMS-946559*	
	MPDL3280A*	NSCLC, melanoma, renal cell carcinoma
	MEDI4736*	NSCLC, other solid tumors
TIM-3	Anti–TIM-3 antibody†	
LAG-3	Dual anti–LAG-3/anti–PD-1 antibody†	
TIGIT	Anti-TIGIT antibody†	
BTLA	Anti-BTLA antibody†	
VISTA	Anti-VISTA antibody†	

BTLA indicates B and T lymphocyte associated; BVAF, *b-raf* proto-oncogene; CTLA-4, cytotoxic lymphocyte-associated antigen-4; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte-activation gene 3; NSCLC, non–small-cell lung carcinoma; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; and VISTA, V-domain Ig suppressor of T-cell activation.

*In testing.

†In development.

syndrome and more widespread use of ICIs.[181] Early data suggest that ICI-associated myocarditis is a class effect and not specific to one therapy; however, when ICIs are used in combination, there is an increased risk of events.[178,181]

More recently, ICIs have been associated with other cardiovascular complications, including myocarditis, pericarditis, vasculitis, and arrhythmias.[170] Existing clinical practice extrapolates from general myocarditis literature for the diagnosis of ICI-associated myocarditis.[171] Diagnosis should be made with a combination of biomarkers (specifically cTn), cardiac imaging, and biopsy.[169] Early data suggest that a significant portion of patients with ICI-associated cardiomyopathy may have normal ejection fraction on an echocardiogram.[178–180] Other cardiac imaging (eg, CMR imaging) and EMB may be necessary to make a prompt diagnosis. In addition, given concomitant myositis in a substantial number of cases of ICI-associated myocarditis, workup for myositis, including checking for creatine kinase and possibly skeletal muscle biopsy, should be performed in suspected patients.[172]

Treatment of ICI-associated myocarditis remains empirical because of a lack of prospective studies. The use of the ICI should be discontinued, and in cases of life-threatening (grade 4) or severe (grade 3) events, reinitiation of ICI is not recommended because of an increased risk for recurrence. Treatment strategies extrapolate from the management of other immune-related adverse events resulting from ICIs via immune suppression.[177] Early use of intravenous corticosteroids is indicated to reduce the risk of progression to fulminant disease with hemodynamic compromise.[169] Although a retrospective study has advocated for higher doses of solumedrol—a methylprednisolone dose of 1000 mg/d for at least 3 days[180]—a definite dose of treatment has not been established. A recent American Society of Clinical Oncology guidelines statement suggested administration of high-dose corticosteroids (1–2 $mg \cdot kg^{-1} \cdot d^{-1}$) initiated rapidly.[173] Although infliximab has been used as adjunctive therapy for other immune-related adverse events, it has been associated with heart failure and should generally be avoided.[174] In patients who are unstable and do not respond to corticosteroids, antithymocyte globulin or intravenous immunoglobulin can be considered.[169] In stable patients who do not respond to corticosteroids, additional immunosuppression with tacrolimus or mycophenolate mofetil can be considered on the basis of their efficacy in treating cardiac allograft rejection.[175] The duration of immunosuppressant treatment is unclear, and it is reasonable to continue until symptom resolution, recovery of LVEF, or cessation of conduction abnormality. Given the risk of arrhythmias, including conduction disease with ICI-associated myocarditis,

Table 7. Major Myocarditis Subtypes Resulting in a Fulminant Presentation

Subtype	H&E Findings	Clinical Manifestations	Treatment
Fulminant lymphocytic myocarditis	Extensive dense lymphocytic infiltrate with associated myonecrosis. May have occasional isolated multinucleated giant cells or eosinophils.	Acute heart failure rapidly leading to cardiogenic shock, conduction abnormalities, or ventricular arrhythmias/SCD. Chest pain.	Treatment is primarily supportive; circulatory support as needed to prevent MOSF. Some evidence that in the absence of cardiotropic viral genome by PCR, steroids may be helpful
GCM	Extensive mixed inflammatory infiltrate characterized by the presence of several multinucleated giant cells (usually present after 1–2 wk), eosinophils, monocytes, and macrophages in the absence of noncaseating granulomas. Edema and extensive myonecrosis often present.	Acute heart failure caused by systolic dysfunction, myocardial restriction, or both. Conduction abnormalities, including CHB and EMD; ventricular arrhythmias, including sustained VT/VF and SCD. Tends to comigrate with other autoimmune diseases.	Treatments consists of multimodality therapy and should be implemented after a tissue diagnosis has been confirmed. Usual therapy includes a combination of a high-dose steroids, a calcineurin inhibitor (such as cyclosporine), and an antimetabolite such as azathioprine. Cytolytic therapy (purified rabbit-derived polyclonal IgG directed at human thymocytes) used for suppression of life-threatening GCM has been reported.
Acute NEM	Extensive inflammatory infiltration of the myocardium with mononuclear cells and eosinophils. Associated myonecrosis or fibrosis. On EM, may see eosinophil degranulation and deposition of major basic protein.	Acute heart failure/cardiogenic shock. May present with a restrictive cardiomyopathy. Prothrombotic intracardiac state. Peripheral eosinophilia may or may not be present. Recent viral infection or new medication.	Identify potential precipitant, especially if a drug hypersensitivity (Table 5). High-dose steroids. Anticoagulation. Often presents with ST-segment elevations and chest pain mimicking an ST-segment–elevation myocardial infarction. Rapid angiography, EMB with subsequent circulatory support, and initiation of high-dose intravenous corticosteroids can be lifesaving.
ICI myocarditis	Newly identified lymphocytic myocarditis resulting from the introduction of novel chemotherapeutic agents that unleash inhibited antitumor T cells, which also may infiltrate and attack the myocardium. Histopathology consistent with lymphocytic infiltrate and myocardial necrosis.	Acute heart failure, cardiogenic shock, and atrial fibrillation developing soon after ICI therapy is started and generally more severe with combination ICI therapy. Typically occurs early in treatment and has a fulminant course.	Treatment includes immediate cessation of therapy, high-dose corticosteroids (1 g solumedrol intravenously daily for 3 d and then 2 mg/kg prednisone daily to start, followed by a slow wean) and initiation of an angiotensin receptor blocker or sacubitril/valsartan. May initially need MCS.

CHB indicates complete heart block; EM, electron microscopy; EMB, endomyocardial biopsy; EMD, electromechanical dissociation; GCM, giant cell myocarditis; H&E, hematoxylin and eosin; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; MCS, mechanical circulatory support; MOSF, multiorgan system failure; NEM, necrotizing eosinophilic myocarditis; PCR, polymerase chain reaction; SCD, sudden cardiac death; and VT/VF, ventricular tachyarrhythmia/ventricular fibrillation.

supportive mechanical therapies such as a pacemaker should be considered. In the future, mechanistic studies may inform proper risk stratification and optimal management strategies. Recent case reports indicate a possible role for abatacept or alemtuzumab for severe cases of ICI-associated myocarditis.[175a,175b]

CONCLUSIONS AND FUTURE DIRECTIONS

FM is an underdiagnosed syndrome with multiple causes that may respond to pathogenesis-specific immunomodulatory therapy. For example, although most inflammatory FM cases are treated with high-dose steroids, the pathogenetic basis of the FM such as NEM, GCM, or ICI dictates the other therapeutic agents that are likely to be active against the given subtype of FM. Patients who recover from FM should abstain from competitive sports for at least 3 to 6 months because of the risk of ventricular arrhythmias triggered by inflammation. The current ESC scientific statement recommends a minimum of 6 months after symptom onset before evaluation for return to sport.[15] The AHA scientific statement recommends that after 3 to 6 months, patients with normal exercise tolerance test, echocardiogram, and Holter monitor may resume competitive sports..[5] Understanding the fundamental biology leading to a given autoimmune response will help us learn how to more precisely treat these potentially deadly syndromes with a high degree of specificity. The cardinal features include rapidly progressive heart failure and cardiogenic shock, as well as electric instability, including sudden death. Early evaluation and management are important to distinguish FM from other forms of acute circulatory compromise, including ischemic heart disease, stress-induced cardiomyopathy, acute tamponade, and the cardiomyopathy of pregnancy. Individualized management strategies that provide the optimal chance of recovery depend on early recognition usually guided by EMB.

However, the diagnosis should be made rapidly with a high index of suspicion such that full circulatory support can be implemented by an expert team to prevent multiorgan system failure, which increases the risk of death or survival with a severe disability. Patients presenting with FM are not the typical critically ill patients seen in the office or emergency department. They are typically younger and healthier (and hence have a robust immune system), present with atypical manifestations of myocardial ischemia and organ system failure, and often because of their

good health either present late or are recognized late when they finally use up their body's reserve. This is where the greatest opportunity lies: early diagnosis, time to right-sided heart catheterization or EMB, time to transfer to an appropriate shock center, and the ability of frontline clinicians to detect the subtle signs and symptoms of someone with impending hemodynamic compromise or circulatory failure. On a national or international level, recognizing these patients and initiating diagnostic and therapeutic treatment in a timely fashion should be a metric that is followed, perhaps limiting the care of these patients to the regional shock centers that have been proposed in the prior AHA statement on cardiogenic shock.

Clinical trials are underway to examine the role of electrogram and real-time CMR guidance to decrease biopsy sampling error. The use of viral genome analysis and immunohistochemical markers to guide management in FM is becoming more widespread in Europe. Trials of specific antiviral agents and immunophenotype-targeted immunomodulation (in viral genome–negative patients) have been proposed. The safety of EMB is increasing with smaller and more flexible bioptomes. The results of these trials and technical advances will certainly affect the management of FM and, we hope, lead to improved patient outcomes.

Although it is fortunate that FM presentations are rare, this rarity also makes them very difficult to study with standard randomized prospective placebo-controlled clinical trials. Most of the evidence for treatment has been generated by registries, case series, and case reports linked to an understanding of the underlying immunology and pathology on a basic science level. We are becoming increasingly adept at classifying FM on the basis of its histological appearance on hematoxylin and eosin microscopy and electron microscopy. Table 7 reviews the common subtypes of myocarditis leading to FM, histological findings, and potential treatment strategies based on case reports and case series. These are not guideline-based recommendations because the evidence to date is not strong enough to reach the rigor required to be classified as guidelines. Rather, these are considerations for the clinician to review that are based on our expert experience.

ARTICLE INFORMATION

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Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Robb D. Kociol‡	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Leslie T. Cooper	Mayo Clinic	NHLBI (HL-135165-03 Autoimmune Mechanisms in Human Myocarditis)†	Myocarditis Foundation (volunteer [unpaid] board member)*	None	None	None	None	None
James. C. Fang	University of Utah	None	None	None	None	None	None	None
Javid J. Moslehi	Vanderbilt University Medical Center	Bristol Myers Squibb (database for ICI myocarditis)†; NIH – R56 141466†, R01 141466†; Pfizer (myocarditis adjudication)†	None	None	None	None	Audentes*; AstraZeneca*; Bristol Myers Squibb*; Deciphera*; Myokardia*; Novartis*; Pfizer*; Regeneron*; Takeda*	None

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Writing Group Disclosures Continued

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Peter S. Pang	Indiana University	Abbott†; Orthodiagnostics†; Roche† (all 3 clinical research); AHA†; AHRQ†; BMS (clinical trial)†; NIH/NHLBI†; Novartis (research study)†; PCORI†	None	None	Loggans and Associates*	None	Baxter*; BMS*; Darma (unpaid)*; Heart Initiative (unpaid)*	None
Marwa A. Sabe	Beth Israel Deaconess Medical Center, Harvard Medical School	None	None	None	None	None	None	None
Ravi V. Shah	Partners HealthCare, Massachusetts General Hospital	NIH†	None	None	None	None	Amgen*; Best Doctors†; MyoKardia†	None
Daniel B. Sims	Montefiore Medical Center, Albert Einstein College of Medicine	None	None	None	None	None	None	None
Gaetano Thiene	University of Padova (ITALY)	None	None	None	None	None	None	None
Orly Vardeny	University of Minnesota Medical School	None	None	None	None	None	None	None

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*Modest.

†Significant.

‡While working on this Scientific Statement as the Writing Group Chair, Dr. Kociol was serving in an academic faculty position at Beth Israel Deaconess Medical Center and Harvard Medical School. Dr. Kociol is now employed by Boehringer Ingelheim Pharmaceuticals, Inc. None of the opinions or recommendations in the AHA Scientific Statement represent those of Boehringer Ingelheim.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Douglas L. Mann	Washington University in St. Louis	None	None	None	None	None	None	None
Frederick J. Schoen	Brigham and Women's Hospital and Harvard Medical School	None	None	None	None	None	None	None
Ryan J. Tedford	Medical University of South Carolina	None	None	None	None	None	Merck*; Actelion*; Abbott*; Arena*: Abiomed†	None

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†Significant.

APPENDIX

The Microbiology and Immunology of Lymphocytic Myocarditis

The initial clinical presentation of any FM has been described earlier in this document. With respect to lymphocytic myocarditis, many viruses have been associated with lymphocytic myocarditis, but bacterial, protozoal, and fungal causes have been described (Figure 1).[182] However, equivocation about these relationships exists because direct evidence is often lacking in many reports, which have depended on either systemic or myocardial evidence for viral infection and have therefore been generally associative. In these studies, concomitant or previous unrelated infection cannot be entirely ruled out. Early studies focused on enteroviruses such as the coxsackie family; more recent reports suggest that hematoviruses such as parvovirus (B19) and human herpes viruses (HHV6) are more common.[183–185] Other implicated viruses have included

adenovirus, influenza A, cytomegalovirus, Epstein-Barr virus, and hepatitis C. In the case of HIV, it should be noted that the virus may not be directly cardiotoxic and the associated myocarditis is mediated through other mechanisms, including coinfection.[186–189] Diversity of the implicated viruses and those affected reflects differences in populations, environmental triggers, and infectious agent epidemiology.

It is likely that cardiotropic viruses such as coxsackievirus[190] result in cardiomyocyte death caused by direct inoculation cardiotoxicity and subsequent processes that invoke indirect cardiomyocyte injury.[98,99] Virus-related injury in lymphocytic myocarditis has been divided into 3 phases: direct viral cardiomyocyte injury, an acute innate immune response, and a virus-specific chronic adaptive immune cascade. In the case of coxsackievirus, direct entry into cardiomyocytes is facilitated by specific receptors (eg, coxsackie-adenovirus receptor). Once in the cell, viral replication with production of viral proteins follows, leading ultimately to lysis of the cardiomyocyte with release of the replicated virus. One such protein, protease 2A, can also disrupt the dystrophin-glycoprotein complex, leading to sarcolemma dysfunction and cardiomyopathy (as is seen in certain muscular dystrophies); a dilated cardiomyopathy phenotype can be produced by cardiac-selective expression of viral protease 2A.[191–193] In addition, many other proteins important in host cell protein synthesis and signal transduction, as well as cardiomyocyte cell structure and contraction, can be affected through targeted cleavage from this protease and others (eg, protease 3C) that are produced as a direct consequence of the viral infection.[98,99] Noncoding microRNAs also appear to play a role in the direct cytotoxicity of viral infection and the subsequent inflammatory response; for example, microRNA-155 is strongly induced in a mouse model of coxsackie-related myocarditis, and blocking it attenuates the inflammatory response and improves cardiac function.[194]

Innate immunity is activated downstream from the binding of virus to its receptor, leading to clearance of the virus through cytokines such as interferons, interleukins, and tumor necrosis factor.[193,195] The innate immunity alarmin proteins S100A8 and S100A9 have recently been linked to the inflammatory and oxidant injury seen in coxsackievirus B3–related myocarditis and could serve as a therapeutic target in myocarditis.[196] However, the cytokine response itself may lead to cardiac dysfunction through myocardial necrosis and induction of apoptosis. Adaptive immunity follows as viral antigens are processed and presented by antigen-presenting cells to T-helper cells, which results in clonally expanded cytotoxic T cells and other effector cells to eliminate infected cells. Humoral immunity is concomitantly stimulated by the T cell–mediated activation of B cells, resulting in antibodies against various proteins, including cardiomyocyte proteins that are now exposed to circulating immune surveillance, for example, molecular mimicry. Persistent viral infection may amplify this process and has been associated with chronic cardiomyopathy and the presence of anti-myosin antibodies.[147,197,198] It should be recognized that this current mechanistic paradigm for viral lymphocytic myocarditis is derived almost entirely from mouse models using coxsackievirus, and their significance to the human condition remains to be established.

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