Myocarditis: Current Trends in Diagnosis and Treatment

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Myocarditis
Current Trends in Diagnosis and Treatment

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Myocarditis is clinically and pathologically defined as "inflammation of the myocardium." Despite its rather clear-cut definition, the classification, diagnosis, and treatment of myocarditis continue to prompt considerable debate. The more routine use of endomyocardial biopsy has helped to better define the natural history of human myocarditis and to clarify clinicopathological correlations. Clinical presentations of the disease range from nonspecific systemic symptoms (fever, myalgias, palpitations, or exertional dyspnea) to fulminant hemodynamic collapse and sudden death. The extreme diversity of clinical manifestations has made the true incidence of myocarditis difficult to determine. Recent prospective postmortem data have implicated myocarditis in sudden cardiac death of young adults at rates of 8.6% to 12%.[1,2] Furthermore, it has been identified as a cause of dilated cardiomyopathy in 9% of cases in a large prospective series.[3] Recent molecular techniques have facilitated new insights into inflammatory autoimmune processes that affect the myocardium and ultimately result in acute or chronic dilated cardiomyopathy.

Despite the well-established morbidity and mortality associated with myocarditis,[4–7] clinical practice guidelines with regard to its evaluation and treatment are lacking.[8] The wide variety of etiologies implicated in myocarditis and its heterogeneous clinical presentations[5,7,9] have impeded patient identification and consensus on the most appropriate diagnostic criteria. The Dallas pathological criteria, published in 1986, served as the first attempt to develop standardized diagnostic guidelines for the histopathological classification of myocarditis.[10] Active myocarditis is characterized by an inflammatory cellular infiltrate with evidence of myocyte necrosis (Figure 1), whereas borderline myocarditis demonstrates an inflammatory cellular infiltrate without evidence of myocyte injury (Figure 2). The inflammatory infiltrate should be further described as lymphocytic, eosinophilic, or granulomatous (Figure 3). The amount of inflammation may be mild, moderate, or severe, and its distribution may be focal, confluent, or diffuse, respectively. A retrospective study of 112 consecutive patients with biopsy-confirmed myocarditis at the Massachusetts General Hospital demonstrated the following pathological distribution: lymphocytic 55%, borderline 22%, granulomatous 10%, giant cell 6%, and eosinophilic 6%.[11]

Sampling error remains a significant limitation to the diagnostic accuracy of the endomyocardial biopsy (EMB). Although 4 to 6 biopsy samples are routinely performed during a diagnostic procedure, a careful postmortem analysis of proven myocarditis cases demonstrated that >17 samples were necessary to correctly diagnose myocarditis in >80% of cases.[12] Because this number of biopsies is not feasible in clinical practice, the lack of sensitivity of EMBs is apparent. Intraobserver variability is another significant limitation in histopathological diagnosis.[13] Parillo[14] and other investigators have asserted that these traditional histopathological criteria should no longer be considered the gold standard for diagnosing myocarditis.

Lieberman et al[15] proposed a broader clinicopathological classification to incorporate the varied clinical features of the disease. This classification divides myocarditis into fulminant, subacute, chronic active, and chronic persistent subtypes. Although these categories extend the definition of myocarditis beyond the narrow confines of the Dallas criteria, this classification is now seldom used. Advances in molecular techniques have demonstrated the presence of viral genome in the myocardium of a significant percentage of patients presenting with unexplained dilated cardiomyopathy, irrespective of whether the Dallas criteria for myocarditis are met.[16] It is now well recognized that the incidence of myocarditis diagnosed by standard hematoxylin-eosin criteria is underestimated when broader criteria that include immunoperoxidase staining of human leukocyte antigens (HLAs) are considered.[17] These newer techniques now permit more accurate identification of patients with inflammatory cardiomyopathy due to unrecognized myocarditis.

Etiologies

Although a broad array of etiologies have been implicated as causes of myocarditis (Table 1), viral myocarditis remains the prototype for the study of the disease and its evolution. Enteroviruses, specifically Coxsackie group B serotypes,[16] have traditionally been perceived as the predominant viral cause. Early studies suggested a causal relationship between symptomatic presentation and rising serum Coxsackie B viral

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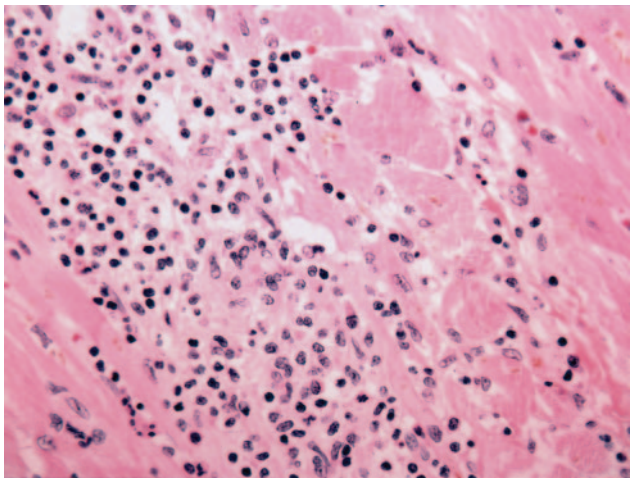

Figure 1. The pathological diagnosis of lymphocytic (viral) myocarditis requires the presence of a lymphocyte-rich inflammatory infiltrate associated with myocyte degeneration or necrosis. The infiltrate is typically predominantly lymphocytic, with lesser amounts of plasma cells, macrophages, and neutrophils. The features of the injury and inflammatory infiltrate should be distinct from those of ischemic injury and toxic injuries such as catecholamine myocardial toxicity. The inflammatory infiltrates of lymphocytic myocarditis are typically not rich in eosinophils, the presence of which would suggest other entities including hypersensitivity myocarditis. Endomyocardial biopsy with hematoxylin and eosin; magnification ×400. Text and image courtesy of James R. Stone, MD, PhD.

titers.[18] However, Keeling et al[19] subsequently reported similar levels of serotype-specific Coxsackievirus B IgM antibodies in household contacts and myocarditis cases. Molecular techniques such as polymerase chain reaction (PCR) have facilitated extensive testing of myocardial tissue for potential viral etiologies.[20–22] Nested PCR analyses of adult and pediatric myocardium have demonstrated the presence of adenoviral genome in patients with idiopathic left ventricular dysfunction with a greater frequency than enterovirus.[23,24] Hepatitis C has been more frequently reported in Japanese patients, whereas parvovirus B19 genome is more commonly identified via nested PCR techniques in German cases.[24–26] Kuhl et al[27] have reported identification of ≥2 different viral genomes in >25% of cases when genome could be amplified. These findings suggest that age-related and regional differences in viral etiology may be more important in the causation of acute and chronic myocarditis than previously appreciated.

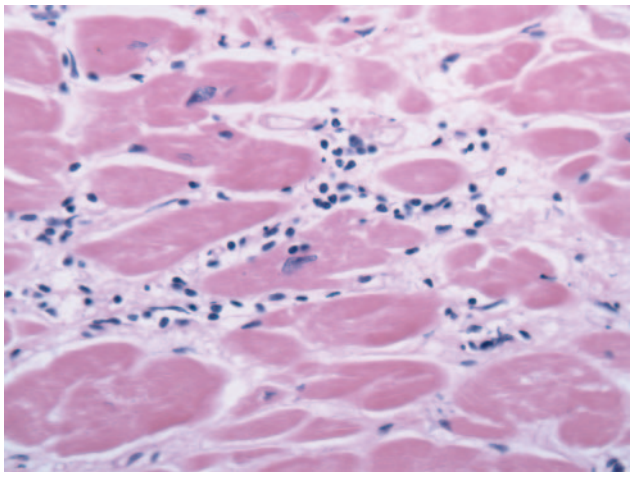

Figure 2. The presence of a lymphocytic infiltrate without associated myocyte degeneration or necrosis is not diagnostic of lymphocytic myocarditis and is typically described as "borderline myocarditis." The pathological features of borderline myocarditis are not specific; because of sampling error, other entities such as sarcoidosis and catecholamine toxicity could be responsible for the pathological findings. Endomyocardial biopsy with hematoxylin and eosin; magnification ×400. Text and image courtesy of James R. Stone, MD, PhD.

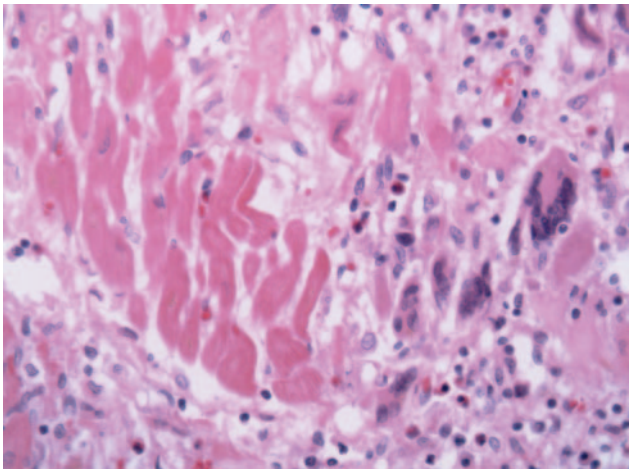

Figure 3. Giant cell myocarditis is a rare disorder characterized pathologically by the presence of a mixed inflammatory infiltrate containing lymphocytes, plasma cells, macrophages, and eosinophils along with numerous giant cells. In the active phase of the disease, the giant cells are typically located immediately adjacent to necrotic cardiac myocytes. Granulomas are typically not present. Giant cell myocarditis must be distinguished from more common disorders that may contain giant cells, including sarcoidosis and hypersensitivity myocarditis. Endomyocardial biopsy with hematoxylin and eosin; magnification ×400. Text and image courtesy of James R. Stone, MD, PhD.

Hepatitis C virus (HCV) has also been associated with myocarditis by identification of HCV antibodies and RNA in sera and cardiac tissue of patients with biopsy-proven myocarditis.[25,28] The causative relationship between HCV infection and dilated cardiomyopathy remains ambiguous; increased tumor necrosis factor (TNF) and cytokine expression have been implicated.[29]

Bowles et al[24] conducted a multicenter study of 624 patients with biopsy-proven myocarditis (66%) or borderline myocarditis (34%). Evidence of viral genome (adenovirus, enterovirus, and cytomegalovirus in decreasing frequency) was identified in 239 (38%) of subjects' endomyocardial biopsies. Thus, contemporary molecular techniques have substantiated the long-held perception that viral infection plays a key role in the development of active myocarditis.

Human immunodeficiency virus (HIV) has been associated with cardiotropic viral infection resulting in myocarditis and left ventricular dysfunction. In a postmortem study of HIV-infected patients, 14 of 21 patients (67%) had myocarditis by histopathological criteria.[30] In another study, EMB of patients with advanced HIV disease and global left ventricular dyskinesis detected myocarditis in 17 of 33 subjects (52%).[31]

TABLE 1. Major Etiologies of Myocarditis*

Viral	
	Adenovirus
	Coxsackievirus
	HCV
	HIV
Bacterial	
	Mycobacterial
	Streptococcal species
	Mycoplasma pneumoniae
	Treponema pallidum
Fungal	
	Aspergillus
	Candida
	Coccidiodes
	Cryptococcus
	Histoplasma
Protozoal	
	Trypanosoma cruzi
Parasitic	
	Schistosomiasis
	Larva migrans
Toxins	
	Anthracyclines
	Cocaine
	Interleukin-2
	Cocaine
Hypersensitivity	
	Sulfonamides
	Cephalosporins
	Diuretics
	Digoxin
	Tricyclic antidepressants
	Dobutamine
Immunologic syndromes	
	Churg-Strauss
	Inflammatory bowel disease
	Giant cell myocarditis
	Diabetes mellitus
	Sarcoidosis
	Systemic lupus erythematosus
	Thyrotoxicosis
	Takayasu's arteritis
	Wegener's granulomatosis

*Adapted with permission from Dec.[67]

HIV-related myocarditis is associated with a significantly poorer prognosis than is lymphocytic myocarditis; multivariate modeling has identified HIV-related myocarditis as the strongest predictor of death among a large cardiomyopathy population.[32] A prospective study of asymptomatic HIV-infected patients revealed a mean annual incidence of progression to dilated cardiomyopathy of 15.9 cases per 1000 patients.[33] The incidence was higher among patients with $CD4^+$ counts <400 cells/mm^3. Histological evidence of myocarditis was detected in 63 of 76 (83%) of these high-risk patients. In situ hybridization identified HIV-infected myocytes in 58 of 76 (76%) of this population.[33] It is often unclear clinically whether the HIV virus itself, medications used for its treatment, or myocardial coinfection is responsible for the observed left ventricular systolic dysfunction. Furthermore, the long-term effects of intensive antiretroviral treatment for HIV myocarditis and its clinical sequelae are undergoing additional study.

Smallpox vaccination has recently been recognized as causing myopericarditis. Cases have been identified by their close proximity to smallpox vaccination (4 to 30 days), clinical manifestations, and elevation of cardiac biomarkers. The Department of Defense Smallpox Vaccination Clinical Evaluation Unit identified a significantly increased incidence of myocarditis after widespread vaccination in late 2002.[34] Individuals without prior vaccine exposure had higher rates of the syndrome, with a reported incidence of 7.8 cases per 100 000 vaccine administrations.[35] One case of eosinophilic myocarditis has been confirmed by endomyocardial biopsy.[36]

Numerous medications have been implicated in hypersensitivity myocarditis including antidepressants[37] (tricyclics), antibiotics[38] (penicillins, cephalosporins, sulfonamides), and antipsychotics[39] (clozapine). A hypersensitivity reaction may be heralded by fever, peripheral eosinophilia, sinus tachycardia, and a drug rash that occurs days to weeks after administration of a previously well-tolerated agent. Myocardial involvement varies but usually does not result in fulminant heart failure or hemodynamic collapse; symptoms recede with drug cessation with or without administration of corticosteroids. EMB typically reveals variable degrees of histiocytic, eosinophilic, lymphocytic, or occasionally granulomatous infiltration; surprisingly, a poor correlation exists between the degree of myocardial inflammation or necrosis and the likelihood of arrhythmias or hemodynamic collapse.[38] Eosinophilic necrotizing myocarditis may represent an extreme form of hypersensitivity myocarditis that rapidly results in cardiovascular deterioration and circulatory collapse.[37]

Autoimmune diseases that are associated with active myocarditis include celiac disease[40] and Whipple's disease[41]; rheumatoid diseases such as systemic lupus erythematosus,[42] mixed connective tissue disease,[43] and systemic sclerosis[44]; and certain hematologic abnormalities such at thrombocytopenic purpura.[45]

Pathogenesis

Our current understanding of the pathogenesis of myocarditis derives largely from animal models. Three essential pathways have been elucidated.[46] Direct myocardial invasion by cardiotropic virus or other infectious agents rapidly progresses to a second phase of immunologic activation. In the last phase, $CD4^+$ activation prompts clonal expansion of B cells, resulting in further myocytolysis, additional local inflammation, and production of circulating anti-heart antibodies.[46] All 3 mechanisms may interact within the same host; the predom-

inant pathogenic mechanism may vary according to host defenses and the specific infectious agent.

During the period of active viremia, cardiotropic RNA viruses such as Coxsackie B or encephalomyocarditis virus are taken into myocytes by receptor-mediated endocytosis and are directly translated intracellularly to produce viral protein.[47] Viral genomic persistence via incorporated double-stranded RNA may also contribute to myocyte dysfunction by cleaving dystrophin or eukaryotic initiation factor-4. The next phase is characterized by inflammatory cellular infiltration, including natural killer cells and macrophages, with the subsequent expression of proinflammatory cytokines, particularly interleukin-1, interleukin-2, TNF, and interferon-γ.[48,49] TNF activates endothelial cells, recruits additional inflammatory cells, further enhances cytokine production, and has direct negative inotropic effects.[50] Cytokines also activate inducible NO synthase (NOS) in cardiac myocytes.[51] The role of NO in the development and progression of myocarditis is complex. NO can inhibit viral replication by targeting specific viral proteases, and peroxynitrate formation has potent antiviral effects.[52] Mice deficient in NOS have greater viral titers, a higher viral mRNA load, and more widespread myocyte necrosis.[53] Conversely, in experimental myosin-induced autoimmune myocarditis, NOS expression in myocytes and macrophages is associated with more intense inflammation, whereas NOS inhibitors have been shown to reduce myocarditis severity.[51,54] Cell-mediated immunity also plays an important role in viral clearing. Cytotoxic ($CD8^+$) cells recognize degraded viral protein fragments that are presented by major histocompatibility-complex class I antigens on the myocyte surface.[55] Finally, circulating autoantibodies directed against contractile, structural, and mitochondrial proteins have been described in both murine and human myocarditis. One or more autoantibodies have been observed in 25% to 73% of patients with biopsy-proven disease.[56] These autoantibodies may have direct cytopathic effects on energy metabolism, calcium homeostasis, and signal transduction; they also can induce complement activation, leading to lysis of antibody-coated cells.[57] Removal of circulating autoantibodies by immunoadsorption has been shown to improve cardiac function and decrease myocardial inflammation.[58–60] It is now hypothesized that normal immunoresponsiveness facilitates viral clearing and allows healing to occur, whereas abnormal immunologic activity can alter the delicate balance by promoting either ineffective viral clearance or favoring persistent T-cell and/or antibody-mediated myocyte destruction.[48,50,61]

HIV myocarditis may result from a similar pathogenic mechanism because virus has been identified within myocytes and is associated with disruption of myocyte integrity and replacement with endocardial fibrosis.[62] In addition, a secondary form of myocarditis may result from direct invasion by toxoplasmosis, candidiasis, aspergillosis, or *Cryptococcus*; all have been associated with HIV coinfection.

Giant cell myocarditis is a rare disorder of uncertain etiology that results in progressive acute or subacute heart failure, is often rapidly lethal, and is diagnosed by the presence of multinucleated giant cells on biopsy.[63] Studies of human tissue with the use of electron microscopy have failed to identify specific viral or other infectious agents.[63] Animal and human models have increasingly implicated an autoimmune pathogenesis, as supported by isolation of macrophage antigens from giant cells along with prominent T-cell lymphocytic proliferation in the surrounding myocardium.[63,64]

The relationship of myocarditis to idiopathic dilated cardiomyopathy has been partially clarified by molecular techniques. Detection of viral RNA at early, intermediate, and late stages of myocardial infection has been demonstrated in animal models of myocarditis, particularly those produced by Coxsackievirus B3.[65] The presence of low levels of ongoing viral replication may result in continued myocardial damage, including apoptotic cell death, as a component of the immunologic response to infection.[48] The presence of HIV- and HCV-infected myocytes at autopsy argues that these infections are capable of producing ongoing myocardial injury that ultimately results in an acute or chronic dilated cardiomyopathy.[33,66]

Clinical Presentation

Clinical manifestations range from asymptomatic ECG abnormalities to cardiogenic shock.[67] Transient ECG abnormalities suggesting myocardial involvement commonly occur during community viral endemics; most patients remain entirely asymptomatic. In contrast, myocarditis can also result in fulminant heart failure presenting as new-onset cardiomyopathy. Patients may report a viral prodrome of fever, myalgias, respiratory symptoms, or gastroenteritis followed by an abrupt onset of hemodynamic collapse. The incidence of a reported infectious viral prodrome is highly variable, ranging from 10% to 80% of patients with documented myocarditis.[6,16,50]

Acute dilated cardiomyopathy is one of the most dramatic and clinically relevant presentations of acute lymphocytic myocarditis.[7] The link between clinical myocarditis and acute dilated cardiomyopathy is most convincingly provided by EMB findings.[67] The 2 largest biopsy series have confirmed myocarditis in 9% to 16% of cases of new-onset dilated cardiomyopathy.[68,69] The Giant Cell Myocarditis Study Group identified heart failure symptoms as the primary presentation in 75% of patients with giant cell myocarditis.[70] Neither symptoms nor clinical course of myocarditis has been shown to correlate with histopathological features such as the extent of lymphocytic infiltrate or fibrosis.[7]

The classification of Lieberman et al[15] differentiates fulminant from active myocarditis. Fulminant myocarditis, manifested by severe hemodynamic compromise requiring high-dose vasopressor support or mechanical circulatory support, was identified in 15 of 147 patients (10.2%) in the largest prospective study to use this classification system.[5] Fulminant cases were additionally characterized by a distinct viral prodrome, fever, and abrupt onset (generally <3 days) of advanced heart failure symptoms. These patients typically have severe global left ventricular dysfunction and minimally increased left ventricular end-diastolic dimensions. Of note, either borderline or active lymphocytic myocarditis can produce this dramatic clinical presentation.

Myocarditis masquerading as an acute coronary syndrome has also been well described.[9,71,72] Elevated troponin levels

have proven to be a more reliable predictor of myocardial injury than levels of creatine kinase.[73] ECG changes suggestive of acute myocardial ischemia typically may include ST-segment elevation in ≥2 contiguous leads (54%), T-wave inversions (27%), widespread ST-segment depressions (18%), and pathological Q waves (18% to 27%).[9,71] Segmental or global echocardiographic wall motion abnormalities are frequently evident despite angiographically normal coronary anatomy.[71] Sarda et al,[72] using myocardial indium[111]-labeled antimyosin antibody and rest thallium imaging, identified 35 of 45 patients (78%) who presented with acute chest pain, ischemic ECG abnormalities, and elevated cardiac biomarkers as having myocarditis. However, biopsy verification of actual myocarditis was not undertaken in this series. In another series of 34 patients with known normal coronary anatomy presenting with symptoms and ECG changes consistent with an acute coronary syndrome, 11 (32%) of the patients were found to have myocarditis on biopy.[9] Clinicians should consider acute myocarditis in younger patients who present with acute coronary syndromes when coronary risk factors are absent, ECG abnormalities extend beyond a single coronary artery territory, or global rather than segmental left ventricular dysfunction is evident on echocardiography.

Myocarditis can produce variable effects on the cardiac conduction system. Ventricular tachycardia is an uncommon initial manifestation of myocarditis but often develops during long-term follow-up.[74] The Giant Cell Myocarditis Study Group reported an initial incidence of ventricular tachycardia of <5% in a multicenter cohort.[70] Ventricular tachycardia due to either lymphocytic or granulomatous myocarditis may infrequently result in sudden cardiac death.[75]

Diagnostic Evaluation

Biopsy

The Dallas criteria[10] have standardized the histopathological definition of myocarditis. Despite its considerable limitations, yielding diagnostic information in only 10% to 20% of cases,[76] EMB findings remain the gold standard for unequivocally establishing the diagnosis. The largest case series of patients with an unexplained cardiomyopathy used biopsy findings to diagnose 111 of 1230 patients (9%) with myocarditis.[68] Fewer than 10% of 2233 patients with idiopathic heart failure referred to the Myocarditis Treatment Trial[6] had EMBs deemed positive by the Dallas criteria. However, multiple investigators have described strong clinical, ventriculographic, and laboratory evidence of myocarditis among patients with negative biopsies.[7,69] Biopsies performed within weeks of symptom onset have a higher yield than those undertaken when symptoms have been more longstanding. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the treatment of heart failure[77] describe EMB as a class IIb recommendation. Biopsy is generally reserved for patients with rapidly progressive cardiomyopathy refractory to conventional therapeutic management or an unexplained cardiomyopathy that is associated with progressive conduction system disease or life-threatening ventricular arrhythmias. It should also be considered when cardiovascular signs or symptoms develop in a patient with a systemic disease known to cause left ventricular dysfunction[78] (Table 2).

TABLE 2. Indications for Endomyocardial Biopsy*

Exclusion of potential common etiologies of dilated cardiomyopathy (familial; ischemic; alcohol; postpartum; cardiotoxic exposures) and the following:
Subacute or acute symptoms of heart failure refractory to standard management
Substantial worsening of EF despite optimized pharmacological therapy
Development of hemodynamically significant arrhythmias, particularly progressive heart block and ventricular tachycardia
Heart failure with concurrent rash, fever, or peripheral eosinophilia
History of collagen vascular disease such as systemic lupus erythematosus, scleroderma, or polyarteritis nodosum
New-onset cardiomyopathy in the presence of known amyloidosis, sarcoidosis, or hemachromatosis
Suspicion for giant cell myocarditis (young age, new subacute heart failure, or progressive arrhythmia without apparent etiology)

Adapted with permission from Wu et al.[78]

Use of Cardiac Biomarkers

Serum cardiac biomarkers (creatine kinase [CK], troponin I and T) are routinely measured when myocarditis is suspected. CK or its isoform (CK-MB) is not generally useful for noninvasive screening because of its low predictive value. Lauer et al[79] reported that only 28 of 80 patients (35%) with suspected myocarditis had elevated troponin levels. Using a serum troponin T cutoff >0.1 ng/mL, these investigators reported a sensitivity for detecting myocarditis of 53%, a specificity of 94%, a positive predictive value of 93%, and a negative predictive value of 56%.[79] Smith and coworkers[73] also examined the value of troponin I in a subgroup of the Multicenter Myocarditis Treatment trial. Although the sensitivity of an elevated troponin I for the entire group was low (34%), its specificity was high (89%). Not surprisingly, a short duration of symptoms (<4 weeks) was associated with a significantly higher sensitivity for detecting biopsy-proven disease.[73] More importantly, the positive predictive value was acceptable at 82%. Most clinicians now routinely measure either troponin T or I whenever a clinical diagnosis of myocarditis is considered.[80]

An early trial used the erythrocyte sedimentation rate to characterize a population with "reactive" myocardial disease but found its sensitivity and specificity to be extremely low.[81] Other serum immunologic biomarkers have included complement,[82] cytokines,[49] and anti-heart antibodies.[83] None of these approaches has been prospectively validated to accurately screen for biopsy-proven myocarditis.

Immunologic Approaches

Advances in immunology have expanded the diagnostic capabilities of the EMB. Immunohistochemical staining has enabled more precise characterization of infiltrating lymphocytes subtypes[84] and can accurately define and help quantify upregulation of major histocompatibility (MHC) antigens. Some investigators have adopted myocyte-specific MHC expression as an essential criterion for diagnosing inflammatory cardiomyopathy. This approach has greater sensitivity

than the Dallas criteria and has reopened the discussion concerning the true incidence of myocarditis among patients with "idiopathic" dilated cardiomyopathy.[85] Herskowitz et al[86] compared quantitative MHC antigen expression in 13 active myocarditis patients with 8 control patients with other forms of cardiac disease. MHC class I and II expression was increased by 10-fold in the myocarditis cohort. Eleven of 13 myocarditis patients (85%) had either myocyte or microvascular endothelial MHC class I or class II expression compared with only 1 of 8 controls (12%). The sensitivity and specificity of any MHC expression for detecting biopsy-proven myocarditis were 80% and 85%, respectively. This methodology was more recently evaluated in a larger cohort of 83 patients with clinically suspected myocarditis.[17] Surprisingly, these investigators found no correlation between MHC immunostaining and histopathological findings of active myocarditis by Dallas criteria. As discussed by the investigators, MHC expression could represent a more chronic form of myocardial injury and may not be responsible for the patients' clinical presentation. The discordance between these findings is currently unexplained because the staining methods and patient populations appeared to be similar. Despite these shortcomings, biopsy assessment of MHC expression has recently been used to guide therapy of patients with inflammatory cardiomyopathy (see below).[87]

Myocardial Imaging

Noninvasive diagnostic myocardial imaging techniques for detection of myocarditis may include echocardiography, nuclear imaging with gallium[67]- or indium[111]-labeled antimyosin antibodies, and MRI.

Echocardiography is currently recommended in the initial diagnostic evaluation of all patients with suspected myocarditis. Several studies have specifically evaluated the role of transthoracic echocardiography for diagnosing myocarditis.[88,89] Pinamonti et al[88] retrospectively analyzed echocardiographic findings among 42 patients with biopsy-proven myocarditis. Left ventricular dysfunction was commonly observed (69%), but left ventricular cavity enlargement was frequently minimal or absent, consistent with other forms of acute dilated cardiomyopathy. Right ventricular dysfunction was present in only 23% of this cohort. Not surprisingly, patients who presented with chest pain or heart block rather than heart failure almost always had preserved ventricular size and function. Segmental wall motion abnormalities were observed in 64% of patients and included hypokinetic, akinetic, or frankly dyskinetic regions. Reversible left ventricular hypertrophy was noted in 15% of patients and typically resolved over several months. Thus, echocardiographic findings can be varied but relatively nonspecific. Serial studies have been shown to be useful in assessing the response to treatment of several forms of myocarditis. Resolution of marked concentric left ventricular hypertrophy in eosinophilic myocarditis after corticosteroid treatment has been reported.[90]

Although anatomic features on echocardiography (ie, chamber dimensions, ejection fraction [EF], wall motion abnormalities) are insufficient to differentiate myocarditis from other forms of cardiomyopathy, ultrasonic tissue characterization may prove to be more useful. Transmission and reflection of ultrasound energy depends on tissue density, elasticity, and acoustical impedance. Changes in 1 or more of these factors lead to different ultrasonic backscatter and an altered image texture. Lieback et al[91] evaluated mean gray-scale values (indicative of average brightness) in 52 patients with biopsy-proven myocarditis; 12 patients had persistent myocarditis, 9 patients had healed myocarditis but lacked fibrosis, and 17 patients had healed myocarditis and fibrosis. Tissue characterization was highly effective in differentiating myocarditis from healthy control myocardium, with sensitivity and specificity values of 100% and 90%, respectively.[91] However, ultrasonic tissue characterization could not accurately differentiate between idiopathic dilated cardiomyopathy and active myocarditis. More recent techniques, particularly tissue Doppler imaging and myocardial velocity measurements, are better able to characterize tissue changes in acute myocarditis and to monitor changes in these parameters over time. Additional validation studies will be required to determine their clinical utility.

Indium[111]-labeled monoclonal antibody fragments (directed against heavy chain myosin) bind to cardiac myocytes that have lost the integrity of their sarcolemmal membranes and have exposed their intracellular myosin to the extracellular fluid space. Unlike gallium[67], which detects the extent of myocardial inflammation, antimyosin cardiac uptake reflects the extent of myocyte necrosis. Dec et al[92] evaluated the utility of antimyosin imaging in a large cohort of patients with clinically suspected myocarditis. On the basis of EMB, antimyosin uptake was found to be highly sensitive (83%) but only moderately specific (53%) for detecting myocardial necrosis. However, the predictive value of a negative scan was high at 92%. More recently, Margari et al[93] have reported that the presence of both a positive antimyosin scan and a nondilated left ventricular cavity (left ventricular end-diastolic dimension $\leq$62 mm) was highly predictive for detecting myocarditis on biopsy.

Contrast-enhanced MRI appears to be the most promising technique for diagnosing myocardial inflammation and myocyte injury on the basis of small, observational clinical studies. Besides providing anatomic and morphological information, MRI can provide accurate tissue characterization by measuring T1 and T2 relaxation times and spin densities. Because active myocarditis is typically associated with myocyte injury, including edema and cellular swelling, assessment of relaxation times provides a sensitive measure for its detection.[94] Friedrich et al[95] evaluated the diagnostic utility of contrast-enhanced cardiac MRI in 19 patients with suspected myocarditis. Early after presentation, myocardial enhancement was generally focal in distribution (Figure 4A). Global enhancement became prominent during later imaging times (Figure 4B) and returned to baseline within 90 days. Unfortunately, the study did not examine the ability of MRI to differentiate viral myocarditis from other causes of acute dilated cardiomyopathy.

Roditi et al[96] evaluated 20 patients with T1 spin-echo cine MR angiography and gadolinium-enhanced spin-echo imaging. Focal myocardial enhancement was associated with regional wall motion abnormalities in 10 of the 12 patients

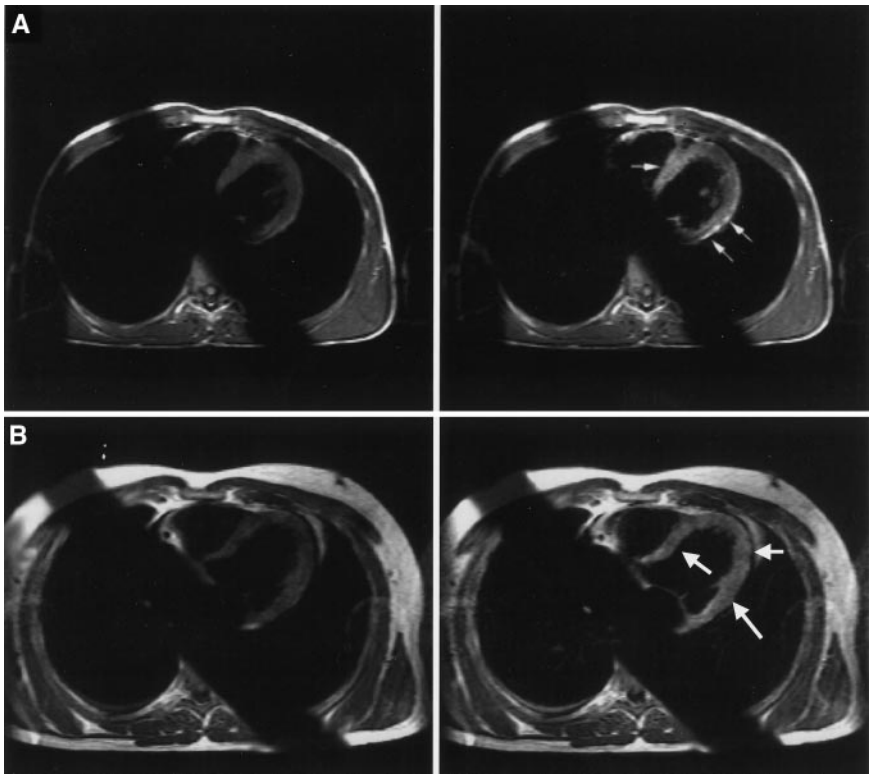

Figure 4. A, T1-weighted MRI cross-sectional views at the midventricular level in a patient with acute myocarditis. Left, Unenhanced view obtained on day 2 after onset of symptoms. There are small foci of increased signal intensity in the subepicardial parts of the posterior myocardium and in the basal septum, which were more evident (right) after administration of gadopentetate dimeglumine (arrows). Reproduced with permission from *Circulation*. 1998;97:1805. B, T1-weighed MRI images obtained before (left) and after enhancement (right) in the same patient as shown in A at 14 days after presentation. More diffuse enhancement of myocardium after gadopentetate dimeglumine, including the apical part of the septum and visible areas of the right ventricle. Reproduced with permission from *Circulation*. 1998;97:1805. © Copyright 1998, American Heart Association.

with suspected or proven myocarditis. The authors concluded that focal myocardial enhancement combined with regional wall motion abnormalities (hypokinesis, akinesis, or dyskinesis) strongly supported a diagnosis of myocarditis. The ability of contrast-enhanced MRI techniques to diagnose other forms of inflammatory heart disease, particularly cardiac sarcoidosis, has also been validated recently.[97]

New contrast MR techniques using segmented inversion recovery gradient-echo pulse sequences and both early and late gadolinium enhancement provide substantial improvement in contrast between diseased and normal myocardium.[98] Mahrholt et al[99] recently used this new technique to perform gadolinium-enhanced MRI-guided biopsy of the right and left ventricles in 32 patients with suspected myocarditis. Left ventricular biopsy was generally performed from the region showing the most marked contrast enhancement. Biopsy of these specific myocardial regions resulted in positive and negative predictive values for detecting myocarditis of 71% and 100%, respectively. MRI may not only be useful in identifying those patients who should undergo biopsy but can also facilitate a guided approach to the abnormal region of myocardium. It is hoped that this focused methodology will improve the sensitivity of EMB for establishing a correct histological diagnosis. Serial MRI studies have also shown promise for tracking the natural history of the disease and could, in the near future, allow noninvasive reassessment of the myocardial response to therapy.

Natural History of Myocarditis

The natural history of myocarditis is as varied as its clinical presentations. Myocarditis masquerading as myocardial infarction almost universally results in a full recovery of cardiovascular status in previously healthy adults.[9,71,72] Individuals with smallpox vaccine–associated myocarditis have also been shown to have rapid resolution of clinical, laboratory, and echocardiographic abnormalities.[100] Patients who present with heart failure may have mildly compromised ventricular function (left ventricular ejection fraction [LVEF] of 40% to 50%) and typically improve within weeks to months. Alternatively, a smaller cohort of patients will present with more advanced left ventricular dysfunction (LVEF $<$35%, left ventricular end-diastolic dimension $>$60 mm). Among this group, 50% of patients will develop chronic ventricular dysfunction, and 25% of patients will progress to transplantation or death; however, the remaining 25% of patients will have spontaneous improvement in their ventricular function.[67,69] A small minority of these patients will present with cardiogenic shock requiring mechanical circulatory support as a bridge to cardiac recovery or transplantation.[101] Somewhat surprisingly, fulminant myocarditis has been described in 1 published series as having the best long-term prognosis with a $>$90% event-free survival rate.[5]

The Myocarditis Treatment Trial reported mortality rates for biopsy-verified myocarditis of 20% and 56% at 1 year and 4.3 years, respectively.[6] These outcomes are similar to the Mayo Clinic's observational data of 5-year survival rates that approximate 50%.[4] Survival with giant cell myocarditis is substantially lower, with $<$20% of patients surviving 5 years[70] (Figure 5).

Predicting prognosis for the individual patient with newly diagnosed cardiomyopathy due to myocarditis remains problematic. Fuse et al[102] evaluated a variety of clinical, hemodynamic, and laboratory parameters in patients with biopsy-proven acute myocarditis. Clinical variables were unable to

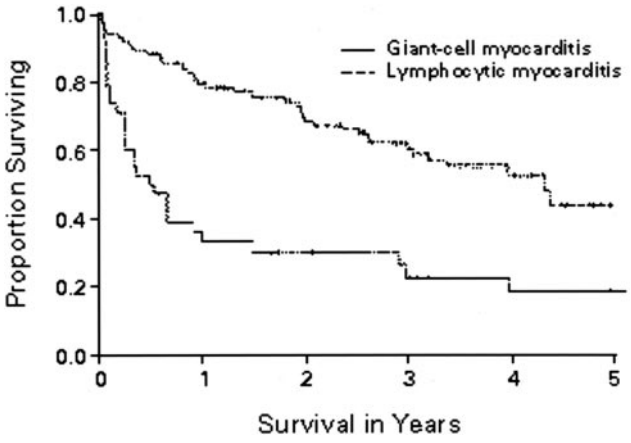

Figure 5. Kaplan-Meier survival curves for 38 patients with biopsy-proven myocarditis and 111 patients with lymphocytic myocarditis enrolled in the Myocarditis Treatment Trial. Duration refers to the time from biopsy diagnosis. $P<0.001$ by log-rank test. Reproduced with permission from Cooper et al.[70]

predict survival. Most significantly, serum levels of soluble Fas and soluble Fas ligand were significantly higher among patients with fatal myocarditis, suggesting that extent of cytokine activation may provide important prognostic information. In a series of biopsy-proven lymphocytic myocarditis cases, Magnani et al[11] used a multivariate predictive model and identified presentation with syncope, bundle branch block, or an EF <40% as significant predictors of increased risk of death or transplantation. Advanced heart failure symptoms (NYHA classes III or IV) and elevated left ventricular filling pressures have also been reported to predict a poorer prognosis.[22] Pulmonary hypertension has also been shown to predict increased mortality in heart failure populations, and this relationship also applies to patients with myocarditis.[103] At our institution,[11] we have demonstrated a survival advantage for patients diagnosed with borderline compared with active myocarditis, but other centers have not found such a clear-cut relationship between histopathology and outcome. Finally, histological resolution of active myocarditis on repeated endomyocardial biopsy has been shown to predict favorable clinical outcome.[104]

Genomic analysis of biopsy specimens has, to date, provided conflicting prognostic information. An initial single-center study of 77 patients by Figulla et al[105] reported a significantly better 4-year transplant-free survival rate for enterovirus-positive (Coxsackie B3 viral genome) patients compared with enterovirus-negative patients (95% versus 55%; $P<0.05$). Furthermore, LVEF increased significantly from 35±13% to 43±9% ($P<0.05$) in the virus-positive group but remained unchanged in the virus-negative group (34±12% to 37±14%; P=NS). In distinct contrast, Why et al[22] detected enteroviral RNA in 34% of 120 consecutive patients with unexplained cardiomyopathy. Enteroviral RNA presence was found to be an independent predictor of adverse outcome. Actuarial survival at 24 months for enterovirus-negative patients was substantially better than that for enterovirus-positive patients (92% versus 68%; $P=0.02$). Most recently, Frustaci et al[106] retrospectively studied 20 patients with lymphocytic myocarditis who failed to respond to immunosuppressive treatment. Of these "nonresponders," 17 of 20 patients (85%) had evidence of viral genome on biopsy. Additional prospective, controlled studies are needed to determine whether genomic analysis can help to predict the likelihood of a therapeutic response to a specific immunosuppressive strategy.

Survival in cardiac sarcoidosis has been shown to be similar to that of lymphocytic myocarditis and idiopathic cardiomyopathy.[107] The prognosis of cardiac sarcoidosis may be further determined by the extent of extracardiac lesions. Patients with giant cell myocarditis have been shown to have the poorest outcomes, with median survival averaging only 5.5 months from the onset of heart failure symptoms or arrhythmias.[70]

Treatment

Supportive care is the first line of treatment. A minority of patients who present with fulminant or acute myocarditis will require an intensive level of hemodynamic support and aggressive pharmacological intervention, including vasopressors and positive inotropic agents, similar to other patients with advanced heart failure due to profound left ventricular dysfunction. Elevated ventricular filling pressures should be treated with intravenous diuretics and vasodilators (when feasible) such as nitroprusside or intravenous nitroglycerin. A ventricular assist device or extracorporeal membrane oxygenation may rarely be required to sustain patients with refractory cardiogenic shock.[108] These devices favorably alter ventricular geometry, reduce wall stress, decrease cytokine activation, and improve myocyte contractile function. Although the data on survival after ventricular assist device or extracorporeal membrane oxygenation implantation are largely observational, the high likelihood of spontaneous recovery of ventricular function argues for aggressive short-term hemodynamic support.

After initial hemodynamic stabilization, treatment should follow current ACC/AHA recommendations for the management of left ventricular systolic dysfunction and include an angiotensin-converting enzyme inhibitor and β-adrenergic blocking agent in all patients and the selective use of an aldosterone antagonist in patients with persistent NYHA functional class III or IV symptoms.[77] The decision to prophylactically implant an implantable cardioverter-defibrillator in patients with advanced left ventricular dysfunction should be deferred for several months whenever possible to allow sufficient time for recovery of ventricular function.

Because the long-term sequelae of viral myocarditis appear to be related to abnormal cellular and humoral immunity, many clinicians believe that immunosuppression should be beneficial for myocarditis treatment.[50] Although >20 uncontrolled observational studies have reported success with the use of a variety of immunosuppressive agents,[109,110] several caveats should be emphasized. First, histological resolution of myocardial inflammation does not closely correlate with improvement in ventricular function. Second, the high incidence of spontaneous improvement in contractile function supports the need for a control group whenever treatment success is evaluated. Finally, the specific viral agent (eg,

adenovirus, enterovirus, or parvovirus) and the immunologic state of the host may result in different response rates to immunosuppression. Despite these considerable obstacles, several controlled clinical trials have been completed successfully (Table 3).

Parrillo et al[81] conducted the first immunosuppressive trial of patients presenting with unexplained dilated cardiomyopathy. Patients were classified as reactive or nonreactive on the basis of histopathology (fibroblastic or lymphocytic infiltrate), immunoglobulin deposition on EMB, a positive gallium scan, or an elevated erythrocyte sedimentation rate. Reactive patients treated with prednisone (60 mg daily) had a statistically greater likelihood of achieving a predefined end point of an increase in LVEF $\geq$5% at 3 months. This improvement was not sustained at 6 or 9 months because the reactive control group showed comparable spontaneous improvement in function. It should be noted that the prednisone dose was decreased to 60 mg on alternate days in the reactive group after 3 months, and this change may have confounded later end point analyses.

The Myocarditis Treatment Trial[6] randomized 111 patients with biopsy-verified myocarditis to receive placebo or an immunosuppressive regimen of prednisone and either cyclosporine or azathioprine. Analysis compared the placebo group with the combined immunosuppressive cohorts. No difference in mortality was evident between treatment groups; furthermore, the degree of improvement in LVEF at 28 weeks was identical (control, 24% to 36%; immunosuppression, 24% to 36%). Multivariate analysis identified higher initial LVEF, less intensive conventional therapy, and shorter duration of symptoms to be independent predictors of subsequent improvement. These 2 controlled trials suggest that immunosuppression should not be prescribed for the routine treatment of viral myocarditis. Immunosuppression can benefit patients with myocarditis due to systemic autoimmune diseases, particularly lupus erythematosus, scleroderma, and polymyositis. Patients with idiopathic giant cell myocarditis have also been shown to benefit from aggressive immunosuppressive protocols.[70]

Intravenous immune globulin has been used to treat both giant cell and lymphocytic myocarditis in uncontrolled studies.[111,112] The Intervention in Myocarditis and Acute Cardiomyopathy Study[113] was a double-blind, randomized, controlled trial of intravenous immune globulin in 62 patients with recent-onset (<6 months) heart failure and unexplained dilated cardiomyopathy. Myocarditis was detected on EMB in 16% of patients. No treatment-related differences were observed in all-cause mortality or improvement in LVEF at 6 or 12 months. Both groups demonstrated substantial increases in LVEF (>10 EF units) during the study period. The spontaneous increase in LVEF observed in the control group once again limited the ability of a small trial to detect meaningful differences between treatment regimens. Gullestad et al[114] also studied the efficacy of intravenous immune globulin in a randomized trial of 40 patients with chronic (mean duration, 3.5$\pm$0.5 years) rather than acute dilated cardiomyopathy. Biopsy was not performed, and therefore the percentage of patients with myocarditis remains unknown. IgG therapy was associated with a marked increase in serum antiinflammatory markers (eg, interleukin-10, soluble TNF), which correlated with significant improvement in LVEF (26$\pm$2% to 31$\pm$3%; $P<0.01$) at 6 months. These changes were not observed in the control group. The long-term benefit of this treatment strategy remains unknown.

Immunohistochemical studies have recently led to a reformulation of our therapeutic paradigm by focusing on the presence of an inflammatory cardiomyopathy rather than biopsy-proven myocarditis per se.[115,116] Wojnicz et al[87] used HLA expression on endomyocardial specimens to identify an inflammatory cardiomyopathy cohort. A total of 84 patients who demonstrated increased HLA expression and chronic dilated cardiomyopathy were randomized to receive 3 months of placebo or immunosuppression with prednisone and azathioprine. Although no difference was observed in the primary composite end point of death, transplantation, or hospital readmission with 2 years, significant increases in LVEF were noted at 3 months and 2 years only among the immunosuppressive group. Whether increased HLA upregulation on EMB can be used to identify a cohort of patients who are more likely to respond to immunosuppression will require a prospective, controlled trial. Our understanding, based on the results of the trials by Gullestad et al[114] and Wojnicz et al,[87] suggests that immunomodulatory therapy is most likely to benefit patients who have a chronic inflammatory cardiomyopathy, persistent immune activation, and ongoing symptoms despite optimal medical therapy.

A more recent observational analysis[106] examined the role of circulating cardiac autoantibodies and viral genomic expression in a cohort of 41 patients with biopsy-proven active lymphocytic myocarditis who had failed to respond to conventional therapy. All patients were treated empirically with azathioprine and prednisone immunosuppression. Patients were subsequently classified as responders or nonresponders after 1 year of follow-up. Cardiotropic viral genome was present in 17 of 20 (85%) of nonresponders compared with only 3 of 21 responders (14%). In addition, cardiac autoantibodies were found in the sera of 19 of 21 responders (91%) and none of the nonresponders in this study. The lack of randomization and lack of a control group limit the generalizability of these potentially important observations and call for additional studies to evaluate their significance.

Finally, both interferon-α and interferon-β have been described as producing hemodynamic and clinical improvement in dilated cardiomyopathy and myocarditis. Interferon-α benefit was described in a case study[117] and in a single-center, randomized trial comparing its efficacy to placebo or thymomodulin.[118] Although mortality did not differ, LVEF rose significantly more in the treatment than the placebo group. Interferon-β has also been shown to produce benefit in a phase II, single-center study of patients with PCR-detected enteroviral or adenoviral genome on endomyocardial biopsy.[119] Data on the efficacy of interferon-α or -β have yet to be confirmed in large-scale, multicenter clinical trials.

Future Directions and Conclusions

Myocarditis is the end result of both myocardial infection and autoimmunity that results in active inflammatory destruction

TABLE 3. Immunosuppressive Therapy for Myocarditis and Dilated Cardiomyopathy

Clinical Trial (Publication Date)	Study Design	Entry Criteria
Interferon-β treatment of cardiotropic viruses (2003)[119]	Phase II observational study; not blinded, no control group; single center	History of cardiac symptoms for 44±27 mo; endomyocardial presence of adenovirus or enterovirus; no other medical reason for cardiac disease
Immunosuppressive therapy in active lymphocytic myocarditis (2003)[106]	Responders vs nonresponders to conventional and immunologic therapies; retrospective; single center	Active lymphocytic myocarditis; immunosuppressive and conventional treatment for 6 mo with progressive heart failure
Immunosuppression with prednisone and azathioprine vs placebo (2001)[87]	Randomized, placebo-controlled; not blinded; single center	1. Increased expression of HLA molecules on endomyocardial biopsy. 2. Chronic heart failure (≥6 mo) and LVEF ≤40% by echocardiography and radionuclide ventriculography. 3. No evidence of other cardiovascular, renal, or endocrine disease
Intervention in Myocarditis and Acute Cardiomyopathy (2001)[113]	Randomized clinical trial, placebo-controlled; double-blinded; cointerventions not matched; multiple centers	LVEF ≤40%, no other cause of idiopathic dilated cardiomyopathy, ≤6 mo of symptoms. No evidence of giant cell myocarditis, sarcoidosis, or hemachromatosis on biopsy
Immunomodulating therapy with IVIG in chronic heart failure (2001)[114]	Randomized clinical trial, placebo-controlled; double-blinded; single center	LVEF ≤40%, NYHA class II/III, stable and optimized regimen; history of CAD or idiopathic DCM
Myocarditis Treatment Trial (1995)[6]	Randomized clinical trial; not blinded; cointerventions not matched; multiple centers	Histological evidence of myocarditis per Dallas criteria
Interferon-α or thymic hormone (1996)[118]	Randomized clinical trial; not blinded; cointerventions not matched	Histological evidence of myocarditis or idiopathic cardiomyopathy; LVEF <45% by angiography. No other reason for cardiac disease; no evidence of giant cell myocarditis
Prednisone in DCM (1989)[81]	Randomized clinical trial; not blinded; single center; cointerventions discontinued	History of idiopathic DCM and no evidence of other cardiovascular disease
Active myocarditis in acute DCM (1985)[7]	Matched cohort; varied interventions; single center	Heart failure of ≤6 mo secondary to dilated cardiomyopathy; LVEF ≤40%; no cause of DCM identified by biopsy

CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; IV, intravenous; IVIG, intravenous immunoglobulin; LVEDD, left ventricular end-diastolic dimension; and LVESD, left ventricular end-systolic dimension.

TABLE 3. Continued

Cohorts, Subjects (n), and Interventions	Results	Strengths/Limitations
22 patients; group A=enteroviral (14); group B=adenoviral (8). All patients received interferon-ß, 18×10^6 IU weekly by subcutaneous injection for 24 wk	1. Eradication of enterovirus and adenovirus on biopsy. 2. 15/22 (68%) had NYHA improvement by 1 class. 3. Significant improvement in LVEF, LVEDD, and LVESD in all (12) patients with baseline LVEF <50%	1. Only 2 biopsies assessed for histological evidence of myocarditis; no patients had histopathological evidence of active myocarditis. 2. Lack of control group (albeit phase II study). 3. Nonrandomized design
41 patients; group A=responders (21); group B=nonresponders. (21). All patients received conventional therapy plus prednisone and azathioprine	Group A: 3/21 (14%) had viral genome, 19/21 (90%) had circulating cardiac antibodies. Group B: 17/20 (85%) had viral genome, 0/20 had circulating cardiac antibodies	1. Limited sample size. 2. Lack of nonimmunosuppressed treatment group. 3. Retrospective analysis. 4. Lack of negative biopsy as control. 5. Nonrandomized design
84 patients, with chronic heart failure and dilated cardiomyopathy; group A=control (43); group B=immunotherapy (41)	No significant difference in mortality; significant difference in LVEF improvement from 6 mo to 2 y	1. Excluded patients with symptoms <6 mo. 2. No immunohistological control. 3. 61/84 (73%) had no evidence of myocarditis by Dallas criteria. 4. Not blinded despite use of placebo. 5. EF did not normalize in either group.
62 patients; group A=control (29); group B=IVIG, 2 g/kg by IV infusion (33). All patients received conventional therapy	No difference in mortality; no difference in LVEF at 6 or 12 mo after randomization	1. Limited incidence of myocarditis on biopsy (7/62 [11.3%]) and no follow-up biopsies. 2. No difference in normalization of LVEF at 1 y (20/56 ([36%]). 3. Single administration of IVIG with dosage based on pediatric myocarditis study. 4. Did not examine other tissue or humoral indicators of inflammation
40 patients; group A=control (20); Group B= IVIG (19)	Significant decrease in cytokine and immunomodulator levels in treatment group; significant increase in LVEF by >5%	1. Short-term trial; no mortality data provided. 2. No intermediate follow-up of sustainability of results. 3. Small size of study groups limits generalizability and statistical power. 4. Mixed etiologies limit applicability of findings
111 patients; group A=control (47); group B=prednisone and azathioprine or cyclosporine	No difference in mortality at 1 y; no difference in change in LVEF at 28 wk	1. Lack of consensus regarding histopathology; unresolved before analysis. 2. No distinction between patients receiving azathioprine or cyclosporine in analysis. 3. Definition of myocarditis limited to histopathological criteria

38 patients;
group A=control (12);
group B=interferon (13);
group C=thymomodulin (13)
	No difference in mortality. Limited sample sizes precluded statistical comparisons	1. No predefined end point, including use of radionuclide ventriculography at 2 y without prior baseline measurement.
		2. Open-label trial.
		3. Small size of study groups limited statistical power

102 patients; group A=nonreactive (42) per study criteria; group B=reactive (60) per study criteria. Both groups randomized to prednisone vs placebo	No difference in mortality between groups A and B or within either group receiving prednisone vs placebo. Group A: increase in LVEF ≥5% at 3 mo, not sustained at 6 mo; no significant change in other end points. Group B: no significant change in LVEF or other end points	1. Diverse nonspecific criteria to distinguish "reactive" disease. 2. Cessation of cointerventions aside from antiarrhythmic and anticoagulation. 3. Nonspecific entry criterion of history of idiopathic DCM. 4. Only patients described as reactive had follow-up biopsies. 5. Diverse histopathology classified as reactive, fibroblastic (38), or lymphocytic (2) disease
27 patients; group A=negative biopsy (9); group B=positive biopsy (18)	No difference in improvement between groups; no difference in improvement within or between groups receiving immunosuppression	1. Lack of standardized protocol, thus duration of symptoms to biopsy, immunosuppressive regimens, follow-up, and monitoring varied. 2. Small cohort size

of myocytes. Its precise characterization and natural history have been limited by the extraordinary variability of its clinical presentations, laboratory findings, and the diversity of etiologies. The relatively low incidence and difficulties in unequivocally establishing a diagnosis have limited the conduct of large-scale, randomized clinical trials to evaluate treatment strategies.

ECG, echocardiography, measurement of serum troponin, and noninvasive cardiac MRI are warranted for initial diagnostic evaluation. Patients presenting with ST elevations, elevated cardiac markers, and ischemic symptoms should undergo prompt coronary angiography. Myocarditis should be considered in patients who lack evidence of coronary atherosclerosis or other pathophysiological etiologies such as stress-induced cardiomyopathy (takotsubo syndrome). Endomyocardial biopsy should be considered for a highly selected group (<5%) of patients, particularly those with increased myocardial enhancement on cardiac MRI, rapidly progressive cardiomyopathy due to suspected giant cell myocarditis or sarcoidosis, suspected allergic myocarditis, or unexplained ventricular dysfunction in the presence of an autoimmune disease known to affect the myocardium. More precise biopsy localization with the use of MRI targeting combined with more sophisticated analysis of myocardial specimens with the use of immunostaining for HLA expression and detection of viral genomic material by PCR will undoubtedly lead to reconsideration of the diagnostic role of biopsy in unexplained cardiomyopathy in the near future.

Treatment of myocarditis in 2006 remains largely supportive. Immunosuppression has not been shown to be effective as routine treatment for acute lymphocytic myocarditis. Early trials of antiviral therapies, such as interferons, suggest a potential therapeutic role but require further investigation. Currently, the standard of care from acute cardiomyopathy remains hemodynamic and cardiovascular support, including use of ventricular assist devices and transplantation when necessary. Pharmacological therapy should consist of a heart failure regimen demonstrated to improve hemodynamics and symptoms. Although the high rate of spontaneous improvement in acute myocarditis and cardiomyopathy provides some optimism, patients who progress to chronic dilated cardiomyopathy experience 5-year survival rates <50%. Ongoing clinical trials should help to clarify whether immune-modulating strategies can improve this prognosis.

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Disclosures

None.

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