Acute Viral Myocarditis: Current Concepts in Diagnosis and Treatment

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ABSTRACT: Acute myocarditis is one of the most challenging diseases to diagnose and treat in cardiology. The true incidence of the disease is unknown. Viral infection is the most common etiology. Modern techniques have improved the ability to diagnose specific viral pathogens in the myocardium. Currently, parvovirus B19 and adenoviruses are most frequently identified in endomyocardial biopsies. Most patients will recover without sequelae, but a subset of patients will progress to chronic inflammatory and dilated cardiomyopathy. The pathogenesis includes direct viral myocardial damage as well as autoimmune reaction against cardiac epitopes. The clinical manifestations of acute myocarditis vary widely – from asymptomatic changes on electrocardiogram to fulminant heart failure, arrhythmias and sudden cardiac death. Magnetic resonance imaging is emerging as an important tool for the diagnosis and follow-up of patients, and for guidance of endomyocardial biopsy. In the setting of acute myocarditis endomyocardial biopsy is required for the evaluation of patients with a clinical scenario suggestive of giant cell myocarditis and of those who deteriorate despite supportive treatment. Treatment of acute myocarditis is still mainly supportive, except for giant cell myocarditis where immunotherapy has been shown to improve survival. Immunotherapy and specific antiviral treatment have yet to demonstrate definitive clinical efficacy in ongoing clinical trials. This review will focus on the clinical manifestations, the diagnostic approach to the patient with clinically suspected acute myocarditis, and an evidence-based treatment strategy for the acute and chronic form of the disease.

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KEY WORDS: myocarditis, acute myocarditis, inflammatory heart disease, inflammatory cardiomyopathy, heart failure, cardiac arrhythmias

Myocarditis is a non-familial form of heart muscle disease [1]. It is defined as an inflammation of the heart muscle, identified by clinical or histopathologic criteria [2]. A broad range of insults – infectious, autoimmune, toxic, drug-induced/ hypersensitive and vasculitic – have been implicated as causes of myocarditis. In general, the histologic patterns of myocarditis are categorized by the predominant inflammatory cells and can be divided into lymphocytic (including viral and autoimmune forms), neutrophilic (bacterial, fungal, and early forms of viral myocarditis), eosinophilic (hypersensitivity myocarditis or hypereosinophilic syndrome), and granulomatous (cardiac sarcoidosis and giant cell myocarditis). One might also encounter reperfusion-type necrosis, which is seen with reperfusion injury and catecholamine-induced injury. Significant overlap exists among categories of myocarditis, and no finding is specific for a single etiology. Viral myocarditis is the most prevalent etiology and has been extensively studied in both animal models and humans [2,3]. In the 1990s new techniques such as polymerase chain reaction and in situ hybridization have improved our ability to diagnose specific viral pathogens in the myocardium [4].
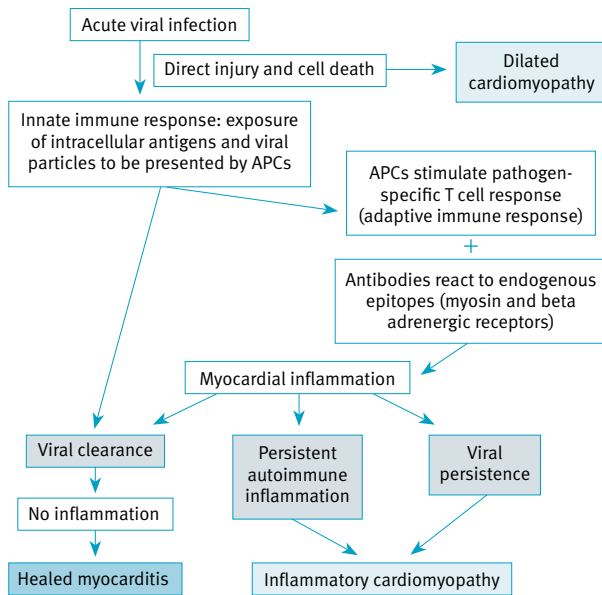
PATHOGENESIS OF THE DISEASE

Myocarditis has largely been studied as a virus-induced autoimmune disease in experimental animal models. A progression from viral myocarditis to dilated cardiomyopathy has long been hypothesized [3].

In the first phase of infection, viremia is followed by direct cardiomyocyte lysis, which activates the innate immune response; this response comprises natural killer cells, interferon-gamma and nitric oxide. Antigen-presenting cells then phagocytize released viral particles and cardiac proteins and migrate out of the heart to regional lymph nodes. Most patients recover following this phase without significant sequelae. A subset of patients progress to a second phase that consists of an adaptive immune response with deleterious effects on the myocardium. In this phase, T cells and antibodies are directed against viral and some cardiac epitopes such as myosin and beta-1 receptors ("anti-heart autoantibodies"), leading to a powerful inflammatory response [5,6]. In most patients, the pathogen is eliminated and the immune reaction is down-regulated. In others, however, the virus or inflammatory process may persist and contribute to the development of "inflammatory cardiomyopathy," a form of dilated cardiomyopathy [Figure 1]. It is now broadly accepted that

Figure 1. Pathogenesis and evolution of acute myocarditis

Figure 2. Evolution of viral causes of myocarditis over time

CVA = coxsackievirus A, CVB = coxsackievirus B, EBV = Epstein-Barr virus, HCV = hepatitis C virus, HHV6 = human herpesvirus 6, PVB19 = parvovirus B19 (From Schultz JC, Hilliard AA, Cooper LT Jr, Rihal CS. *Mayo Clin Proc* 2009; 84 (11): 1001-9. With permission)

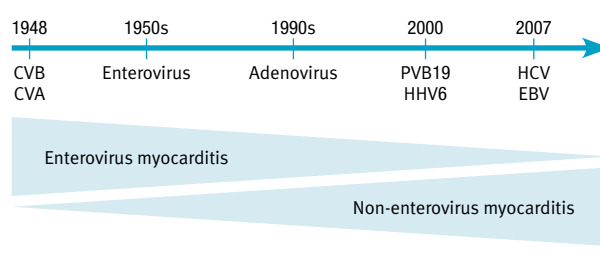viral myocarditis plays a major role in the development of inflammatory cardiomyopathy [1].

Long-term follow-up studies of patients who present with acute myocarditis have shown that approximately 21% of them develop dilated cardiomyopathy [7]. Moreover, the presence of a viral genome was demonstrated by polymerase chain reaction in the myocardium in up to 67% of patients with idiopathic left ventricular dysfunction [8]. Thus, dilated cardiomyopathy can occur as a late stage following cardiac infection and inflammation. In contrast to acute myocarditis, which is predominantly characterized by preserved left ventricular size and normal or even increased wall thickness due to edema, inflammatory cardiomyopathy is characterized by the presence of chronic inflammatory cells associated with left ventricular dilatation, wall thinning and reduced ejection fraction, with or without viral persistence [1,9].

Different mechanisms have been suggested for this evolution – from acute disease to dilated cardiomyopathy [3-8,10]. Both innate and adaptive immune responses are crucial determinants of the severity of myocardial damage. A genetic predisposition has also been hypothesized.

> MRI is emerging as an important tool for the diagnosis and follow-up of patients with acute myocarditis

ETIOLOGY OF ACUTE VIRAL MYOCARDITIS – THE VIRAL SHIFT

In the mid- and late 1990s, enteroviruses, particularly coxsackie B virus, were linked by sero-epidemiologic and molecular studies to outbreaks of acute myocarditis [7,11]. During the following years, however, the prevalence of the enteroviruses

decreased and the prevalence of other viruses increased [12]. Bowles and co-authors [12] isolated a viral genome from 38% of biopsies taken from 624 patients presenting with myocarditis between the years 1988 and 2000. Adenovirus was found to be the most common pathogen, particularly in children. More recently, parvovirus B19 was described as the most prevalent pathogen [8,13,14]. The parvovirus B19 viral load detected in the endothelium of myocardial vessels of patients with acute myocarditis was ten thousand times higher than the load in patients with chronic myocardial inflammation or in controls with no inflammation at all [15], suggesting a direct correlation between viral presence and acute myocarditis. By damaging mainly endothelial cells of the blood vessels, parvovirus B19 often causes acute myocarditis that mimics acute coronary syndrome, with severe chest pain, electrocardiographic ST-T changes, and significant elevation of blood troponin I and T [14]. Hepatitis C antibodies and RNA have been isolated from the sera and myocardium of Japanese patients with myocarditis [16]. Figure 2 presents the shift of viral etiologies of myocarditis over time.

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH IN SUSPECTED ACUTE MYOCARDITIS

Most patients with viral myocarditis are asymptomatic or minimally symptomatic and do not seek medical help. In symptomatic patients, the clinical presentation of viral myocarditis varies from non-specific electrocardiographic abnormalities in the setting of normal left ventricular systolic function to acute hemodynamic compromise or sudden cardiac death. A viral prodrome including fever and respiratory or gastrointestinal symptoms frequently precedes the onset of the disease [17,18]. In 3055 patients with suspected acute or chronic myocarditis who were screened in the European Study of the Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID), 72% of patients had dyspnea, 32% had chest pain, and 18% had arrhythmias [18].

More severe clinical scenarios of acute myocarditis can include acute (usually less than 2 weeks of duration) development of heart failure, with normal-sized or dilated left ventricle and hemodynamic compromise. This is characteristic of active lymphocytic myocarditis, necrotizing eosinophilic myocarditis or, rarely, giant cell myocarditis. A subset of patients presents with fulminant myocarditis, characterized by the rapid onset of symptoms and severe hemodynamic compromise at presentation. These patients often require hemodynamic support for survival. Paradoxically, the long-term survival rate is usually good in fulminant myocarditis if patients survive the initial phase. This is in contrast to acute myocarditis in which the development of symptoms is more protracted and the clinical picture less dramatic, but long-term outcome is worse [19]. A rare type of myocarditis is giant cell myocarditis. It is characterized by heart failure with dilated left ventricle and new ventricular arrhythmias, high degree heart block, and/or lack of response to standard heart failure therapy within 1–2 weeks [20]. Giant cell myocarditis has the worst prognosis of all [20]. Finally, myocarditis can present as acute myocardial infarction-like syndrome, with acute chest pain, tachyarrhythmia, or sudden death, but with normal epicardial coronary arteries [14,21].

Findings on physical examination are variable but may provide insight into the underlying cause. These can include tachycardia, laterally displaced point of maximal impulse, soft S1 sounds, S3 or S4 gallop, lymphadenopathy (sarcoidosis), rash (hypersensitivity), polyarthritis, subcutaneous nodules, or erythema marginatum (acute rheumatic fever).

The sensitivity of the electrocardiogram is low (47%) in myocarditis. The most common electrocardiographic abnormality is sinus tachycardia with non-specific ST-T wave changes [22]. Supraventricular and ventricular arrhythmias can also be seen, as well as disturbances in the conduction system such as atrioventricular and intraventricular (left and right bundle branch) block. Occasionally, a pseudo infarct pattern and ischemic changes are seen. ST segment elevation is commonly seen, but ST segment depression, T wave inversion, poor R wave progression, and Q waves have also been described [21]. The presence of Q waves or bundle branch block is associated with increased rates of heart transplant or death [23]. Several mechanisms may account for the ischemic changes in myocarditis: a) myocardial inflammation may lead to left ventricular mural thrombus and coronary artery embolization, b) vasoactive kinins or catecholamines released during the acute phase of viral infection can lead to coronary artery spasm, and c) arteritis caused by the parvovirus B19 and platelet activation may cause in situ thrombi formation in coronary arteries. Troponin T and I are more sensitive than creatinine kinase MB or histology for the diagnosis of acute myocarditis [16,24].

The indications for endomyocardial biopsy are currently limited to fulminant cases, cases unresponsive to supportive therapy, and those with conduction disturbances and malignant arrhythmias in which giant cell myocarditis has to be ruled out

IMAGING MODALITIES FOR THE DIAGNOSIS OF ACUTE MYOCARDITIS

- **Echocardiography**

Echocardiography is an important component of the diagnostic workup of myocarditis, serving to evaluate LV function and to rule out other causes of heart failure, such as valvular, congenital, or amyloid heart disease. Classic findings include global hypokinesis with or without pericardial effusion. In some cases, segmental wall motion abnormalities can mimic myocardial infarction. Although the echocardiographic features of myocarditis are often non-specific, a careful review of findings may be helpful in suggesting a diagnosis, guiding the acute management and determining prognosis. Felker et al. [9] developed echocardiographic criteria to help distinguish between fulminant and acute myocarditis. Patients with fulminant myocarditis had near normal LV diastolic dimensions and increased septal thickness at presentation, secondary to acute myocardial edema, while patients with acute myocarditis had increased diastolic dimensions. Patients with fulminant myocarditis exhibited a substantial improvement in ventricular function at 6 months as compared to patients with acute myocarditis. In addition, right ventricular systolic dysfunction is a powerful independent predictor of death or need for heart transplantation in patients with myocarditis [25].

- **MRI**

More recently, cardiovascular magnetic resonance imaging has emerged as a highly sensitive and specific tool for the diagnosis of myocarditis [26]. MRI has the unique potential to visualize tissue changes and can detect the characteristic changes in myocarditis including intracellular and interstitial edema, capillary leakage, hyperemia and, in more severe cases, cellular necrosis and subsequent fibrosis.

Tissue edema can be demonstrated by T2-weighted imaging. Hyperemia and capillary leak can be detected by contrast-enhanced fast spin echo T1-weighted MR and early gadolinium enhancement. The intravenously administered contrast material gadolinium (Gd-DTPA) is excluded from the intracellular space of the myocytes by the sarcolemmal membranes. In acute myocarditis, rupture of myocyte membranes enables gadolinium to diffuse into the cells, resulting in an increased tissue-level concentration and subsequent contrast enhancement.

LV = left ventricular

Necrosis and fibrosis, which are the result of irreversible tissue damage, are demonstrated by late gadolinium enhancement. A combined MRI approach using T2-weighted imaging, early and late gadolinium enhancement, provides high diagnostic accuracy and is a useful tool in the diagnosis and assessment of patients with suspected acute myocarditis [26].

MRI can also play a role in discriminating myocarditis from myocardial infarction, which can help in the evaluation of acute chest pain. In myocarditis the infiltrates are characteristically located in the mid-wall and tend to spare the sub-endocardium, whereas in infarction, the sub-endocardium is involved first. Based on the current data, a recently published consensus document on MRI in myocarditis suggests that MRI should be performed in patients with suspected myocarditis who have persistent symptoms, evidence of significant myocardial injury, and if the MRI results are likely to affect clinical management [27]. MRI may also be useful to guide tissue sampling of an endomyocardial biopsy [13].

## ROLE OF ENDOMYOCARDIAL BIOPSY IN THE DIAGNOSIS AND RISK STRATIFICATION OF MYOCARDITIS

In 1987, the Dallas criteria were proposed for standardization of the diagnosis of myocarditis using a histopathologic diagnosis [28]. These criteria require an inflammatory cellular infiltrate with or without associated myocyte necrosis on histopathologic analysis of heart tissue sections. During the subsequent years, these criteria were found to be limited due to sampling error, variation in expert interpretation, variance with other markers of viral infection and immune activation in the heart, as well as the lack of relevance for management and clinical outcome. Thus, the Dallas criteria are no longer considered adequate for state-of-the-art diagnosis and risk stratification of acute myocarditis [29]. Alternative pathologic classifications rely upon cell-specific immunohistological staining for surface antigens, such as anti-CD3 (T cells), anti-CD4 (T helper cells), anti-CD20 (B cells), anti-CD68 (macrophages), and anti-human leukocyte antigen. This technique is associated with less sampling error and is therefore more sensitive than histopathology and may also have better prognostic value [30].

Endomyocardial biopsy is indicated when giant cell myocarditis or necrotizing eosinophilic myocarditis is suspected. Figure 3 presents biopsies taken from two patients who were admitted to our department with acute heart failure and severely reduced LV function. The biopsies provided the basis for the proper diagnosis and treatment [31].

Randomized phase III studies failed to demonstrate the benefit of endomyocardial biopsy-guided management in acute myocarditis. A recently published American Heart

Ongoing clinical trials may provide support for future use of antiviral, immunosuppressive or immunomodulatory therapies in selected subgroups of patients

Figure 3. Examples of patients with acute heart failure in whom endomyocardial biopsy had a central role in diagnosis and proper management (Hematoxylin & eosin staining). The first case [A] was a 76 year old woman with proven severe coronary disease. She was admitted with an initial diagnosis of recurrent acute coronary syndrome and cardiogenic shock. When coronary angiography did not support the diagnosis of a new coronary event, endomyocardial biopsy was performed. The biopsy demonstrated severe, diffuse necrotizing lymphocytic myocarditis with a single giant cell (arrow in insert). Although the differential diagnosis of this specimen includes giant cell myocarditis, the lack of histiocytes and eosinophils did not support this diagnosis. She received supportive therapy and fully recovered [31]. The second case [B] was a 29 year old woman who presented with new-onset severe heart failure. She also developed intermittent complete heart block and non-sustained ventricular tachycardia. The clinical scenario suggested giant cell myocarditis and a biopsy was performed. The biopsy demonstrated acute lymphohistiocytic myocarditis, without evidence of giant cells or eosinophils. She responded to standard treatment. In both cases the final diagnosis was fulminant myocarditis
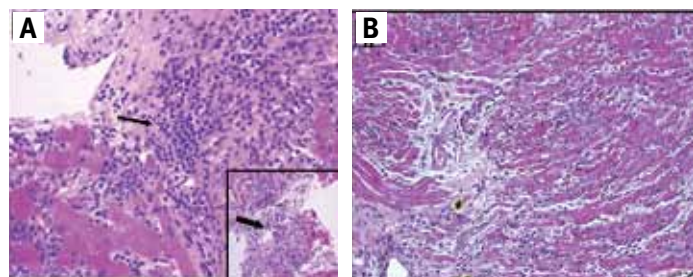
Association/American College of Cardiology/European Society of Cardiology joint statement regarding the indications for endomyocardial biopsy recommends performing a biopsy in scenarios that are compatible with fulminant and giant cell myocarditis, and in acute heart failure unresponsive to treatment [32]. The indications for endomyocardial biopsy may expand if benefit is demonstrated by ongoing clinical trials on dilated cardiomyopathy targeting viral persistence or the inflammatory process [33,34].

TREATMENT

Most patients with acute myocarditis do not require therapy. Patients with left ventricular dysfunction or symptomatic heart failure should follow current heart failure therapy guidelines [35], including the administration of diuretics and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Beta-blockers can be used cautiously in the acute setting. To date, there are no studies to determine if, when and how to discontinue standard heart failure therapy.

For patients with fulminant myocarditis whose condition deteriorates despite optimal pharmacological management, case series suggest a role for mechanical circulatory support, such as intra-aortic balloon pump, ventricular assist devices or extracorporeal membrane oxygenation as a bridge to transplan-

tation or recovery [16]. Patients with acute myocarditis should refrain from strenuous physical activity for a period of at least 6 months following the onset of symptoms. They may return to regular activity only after prudent evaluation to determine that LV dimensions and function have returned to normal on echocardiography, and that no significant arrhythmias are present on exercise testing and 24 hour electrocardiogram Holter monitoring [36,37].

In giant cell myocarditis, immunosuppression is a well-established treatment, since patients with giant cell myocarditis treated with prednisone and cyclosporine had a significantly prolonged transplant-free survival [20]. More recently, the addition of CD-3 muromonab was also tried successfully in these patients [38]. Immunosuppression is also employed in hypersensitivity myocarditis and myocarditis associated with systemic diseases like lupus erythematosus and sarcoidosis. A flow chart of suggested evaluation and treatment of patients with acute myocarditis is presented in Figure 4.

The benefit of treatment other than supportive therapy in acute lymphocytic myocarditis has not been proven. In contrast, in inflammatory cardiomyopathy, additional therapeutic options are currently under investigation. These include antiviral agents, immunosuppressive drugs, and immunomodulation with intravenous immunoglobulins and immunoadsorption.

Interferons serve as a natural defense against many viral infections. Innate production of interferons is associated with clinical recovery from viral infection. Exogenous administra-

tion of IFNβ induces cellular immune response and therefore preferentially affects viruses that directly infect cardiomyocytes (e.g., enteroviruses). Currently, there is no approved treatment for chronic viral heart disease, but data from uncontrolled open-labeled phase II studies have demonstrated significant benefit from IFNβ treatment in subgroups of patients who had not improved with regular heart failure medication and show entero- or adenoviral persistence on endomyocardial biopsies. This was shown even years after the onset of chronic disease [39].

Myocardial inflammatory processes due to pathogenic autoimmunity may continue after myocardial virus elimination. In such cases, immunosuppressive treatment might be effective. The MTT and IMAC trials failed to show benefit for immunosuppression and immunoglobulins beyond supportive therapy in inflammatory cardiomyopathy [17,40]. However, two randomized trials did demonstrate an improvement in New York Heart Association class and LV ejection fraction following immunosuppressive therapy [33,34]. This treatment might represent a double-edged sword, since immunosuppression might facilitate viral replication and therefore might be detrimental in patients with viral persistence in the myocardium. The question whether immunosuppression could be beneficial in "virus-negative" inflammatory cardiomyopathy was addressed in the recently published TIMIC study [34]. This single-center randomized trial included patients with heart failure of at least 6 months duration despite supportive medical therapy, in whom the presence of lymphocytic myocarditis was proven by endomyocardial biopsy and chronic inflammation by immunohistochemistry, but no viral genome persistence on polymerase chain reaction analysis. The patients were randomized to therapy with prednisone and azathioprine versus placebo. Both groups received conventional therapy. The trial showed a marked improvement in LV function at 6 months in the group that received immunosuppressive therapy. The results of this study might represent a turning point in the concept of immunosuppression in inflammatory cardiomyopathy. Larger multi-center randomized trials are needed to evaluate important endpoints such as recurrent heart failure, need for ventricular assist device or transplantation, and death. These clinical endpoints need to be evaluated prospectively because a short-term increase in LV ejection fraction may not necessarily correlate with the long-term risk of death or transplantation in this subset of dilated cardiomyopathy patients.

Figure 4. Flow chart for evaluation and treatment of patients with suspected acute myocarditis
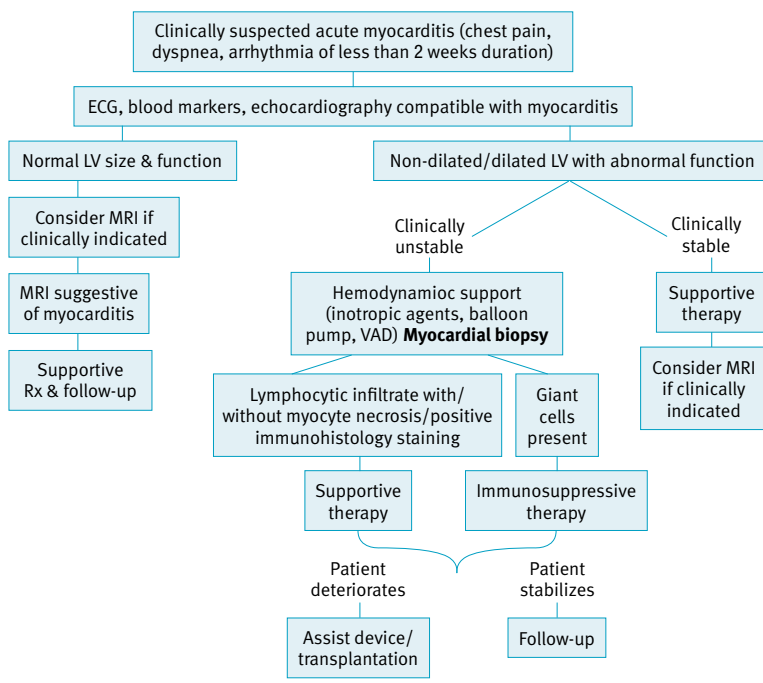
CONCLUSIONS

Acute myocarditis presents multiple challenges in diagnosis and treatment. The pathogenesis is complex and includes direct viral myocardial damage as well as autoimmune reactions against cardiac epitopes. Currently, parvovirus B19 and adenoviruses are emerging as the most prevalent viral pathogens. MRI is

IFNβ = interferon-beta

an important tool for the diagnosis and follow-up of patients with acute myocarditis and perhaps for the guidance of endomyocardial biopsy. Endomyocardial biopsy is limited today to fulminant cases, to cases with conduction disturbances and malignant arrhythmias to rule out giant cell myocarditis, and to cases unresponsive to standard anti-failure therapy. Treatment of acute myocarditis is still mainly supportive with the exception of giant cell myocarditis, hypersensitivity myocarditis, and myocarditis associated with systemic diseases like lupus erythematosus and sarcoidosis. Immunotherapy and specific antiviral treatment have yet to demonstrate definitive clinical efficacy in acute myocarditis. However, ongoing clinical trials may provide additional support for antiviral or immunosuppressive therapies in specific, well-characterized subgroups of patients.

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