The inflammatory cardiomyopathies refer to a broad group of disorders characterized by myocardial inflammation as a primary cause of cardiac dysfunction and must be viewed in contradistinction to a secondary immune response to another mechanism of injury (ie, ischemia or genetic cardiomyopathy). Interestingly, it has recently been shown that cardiac autoantibodies exist in most patients with advanced heart failure, regardless of the pathogenesis; thus, cardiac inflammation per se is a broad pathophysiologic mechanism.1 Even in patients with familial dilated cardiomyopathy, for example, healthy siblings frequently have cardiac autoantibodies present years before the onset of disease.2 Given the ubiquitous role of the immune system in cardiomyopathies and the challenges of creating a comprehensive classification system of cardiomyopathies, the scope of this article will focus on cardiomyopathies that have inflammation as the primary pathological event.

Abstract: Inflammatory activation occurs in nearly all forms of myocardial injury. In contrast, inflammatory cardiomyopathies refer to a diverse group of disorders in which inflammation of the heart (or myocarditis) is the proximate cause of myocardial dysfunction, causing injury that can range from a fully recoverable syndrome to one that leads to chronic remodeling and dilated cardiomyopathy. The most common cause of inflammatory cardiomyopathies in developed countries is lymphocytic myocarditis most commonly caused by a viral pathogenesis. In Latin America, cardiomyopathy caused by Chagas disease is endemic. The true incidence of myocarditis is unknown to the limited utilization and the poor sensitivity of endomyocardial biopsies (especially for patchy diseases such as lymphocytic myocarditis and sarcoidosis) using the gold-standard Dallas criteria. Emerging immunohistochemistry criteria and molecular diagnostic techniques are being developed that will improve diagnostic yield, provide additional clues into the pathophysiology, and offer an application of precision medicine to these important syndromes. Immunosuppression is recommended for patients with cardiac sarcoidosis, giant cell myocarditis, and myocarditis associated with connective tissue disorders and may be beneficial in chronic viral myocarditis once virus is cleared. Further trials of immunosuppression, antiviral, and immunomodulating therapies are needed. Together, with new molecular-based diagnostics and therapies tailored to specific pathogeneses, the outcome of patients with these disorders may improve. (Circ Res. 2017;121:803-818. DOI: 10.1161/CIRCRESAHA.117.310221.)

Key Words: cytokines ▪ gene expression ▪ heart failure ▪ myocarditis ▪ sarcoidosis
The innate and adaptive immune systems are involved in all forms of cardiac injury, including ischemic injury. The innate immune response contains pattern recognition receptors such as toll-like receptors (TLR) that trigger a proinflammatory cascade of cytokines and interferons if they detect pathogen-associated molecular patterns or damage-associated molecular patterns (ie, noninfectious triggers). Neutrophils, macrophages, and natural killer cells are major components of innate immunity. Antigen-presenting cells (ie, dendritic cells and activated macrophages) of the innate immune system help direct much of the response of the adaptive immune system, consisting broadly of T and B lymphocytes.

**Epidemiology**

Viral infections cause the majority of inflammatory cardiomyopathies in the developed world and are the focus of most animal models of myocarditis. However, a broad array of infectious pathogens can lead to inflammatory cardiomyopathies, including bacterial infections and parasites. Finally, noninfectious myocardidites are usually associated with autoimmune disorders, toxins, or hypersensitivity (Figure 1). Data from the global burden of disease study show that in 2015, there were 353,700 worldwide deaths attributed to cardiomyopathy and myocarditis, with an increasing incidence since 2005 but a modest improvement in mortality rate. In children, the most common known cause (ie, after idiopathic) of dilated cardiomyopathy (DCM) is myocarditis, although it should be noted that only slightly more than half of these patients met definite histological criteria—notably the gold-standard Dallas criteria. The true incidence of myocarditis is not precisely known, partly because of the infrequent performance of endomyocardial biopsies and also partly because of the low sensitivity of the Dallas criteria.

**Lymphocytic Viral Myocarditis**

Investigations of children admitted with acute viral illnesses found cardiac abnormalities suggestive of myocarditis in up to one third of patients, indicating that perhaps there may be a high prevalence of subclinical or under-recognized myocarditis. In terms of specific pathogens involved in viral myocarditis, the data vary in part according to geographical location. Among adult German patients with idiopathic DCM undergoing endomyocardial biopsies, parvovirus B19 (PVB19) is the predominant virus, present in just >50% of patients. In the United States, however, adenovirus and enteroviruses have been the most commonly isolated pathogens among myocarditis patients of all ages, whereas parvovirus has typically been rare. More recent analysis of biopsies of pediatric transplant recipients in the United States shows parvovirus as the predominant virus, however, suggesting that there may have been an epidemiological shift in the United States toward a higher parvovirus prevalence. Although this has not been studied in the past decade in a nontransplanted cardiomyopathy population, the prevalence of specific viruses is generally known to be similar between transplanted patients and cardiomyopathy patients. Myocarditis caused by hepatitis C also varies by region, and in Japan, it is more commonly isolated in patients with DCM and hypertrophic cardiomyopathy.

**Clinical**

Lymphocytic myocarditis can present with a broad range of symptoms, including chest pain (with or without associated pericarditis), heart failure, and sudden cardiac death, particularly among younger patients. US registry data found myocarditis to be the third leading cause (6%) of cardiovascular death among young athletes, after hypertrophic cardiomyopathy (36%) and coronary artery anomalies (17%). An Israeli study based on 162 autopsies for patients <40 years of age found that 16% had evidence of myocarditis.

Clinicopathological criteria have been proposed to describe different presentations with variable natural histories: fulminant, acute, chronic active, and chronic persistent. In general, the overall prognosis for patients with myocarditis is similar to other patients with DCM. Additionally, emerging evidence suggest that lymphocytic myocarditis can sometimes preferentially involve the right ventricle (RV), mimicking arrhythmogenic RV dysplasia clinically, only distinguishable by endomyocardial biopsy (EMB) findings of myocarditis or viral replication.

**Pathophysiology: Brief Overview**

Animal models inform much of what is known about the development of myocarditis. Evidence supports the role for direct viral myocardial injury and a pathological inflammatory response. In these models, the virus enters the myocardium, using receptor complexes such as the common receptor for coxsackie and adenoviruses. The innate immune system is activated via TLRs, especially TLR-3 and TLR-4. Natural killer cells and macrophages are activated, and type-I interferon is released in an attempt to clear the virus. The innate immune system subsequently triggers the acquired immune response with T- and B-cell proliferation. T cells may attack both viral proteins and, via molecular mimicry, exposed myocardium such as myosin in an autoimmune fashion. The
release of cardiac myosin from damaged cardiomyocytes acts as a ligand for TLRs and stimulates an ongoing innate inflammatory response. B-cell activation and cardiac autoantibodies (ie, to myosin or β1 adrenergic receptors) contribute to ongoing myocardial inflammation, especially if there is persistence of viral replication. Persistence of the virus in the myocardium is associated with worse outcomes while viral clearance is associated with clinical improvement.

Recently, much has been learned about the role of 2 CD4+ subtypes in myocarditis and other autoimmune conditions. T helper (Th) 17 cells typically produce proinflammatory cytokines (eg, interleukin-17 [IL-17], tumor necrosis factor-α), whereas regulatory T cells (Tregs) typically produce immunosuppressive cytokines such as IL-10 or transforming growth factor β. Peripheral blood from humans with myocarditis show increased TH17 cells and decreased Treg cells. Furthermore, an increase in TH17 cells is correlated with both myocardial fibrosis and worsening New York Heart Association functional classification. Tregs, which help the immune system maintain self-tolerance by preventing excess autoimmune response, have been shown to play a crucial role in animal models of viral myocarditis. Mice injected with Tregs are protected against coxsackievirus-induced myocarditis by decreasing both inflammation and viral load. Also, Treg cells lead to decreased expression of the coxsackie-adenovirus receptor, mediated via increased transforming growth factor β.

Although the pathophysiology of viral myocarditis caused by PVB19 is not as well characterized as that of myocarditis caused by coxsackie or adenoviruses, the existing data demonstrate that the mechanism of myocarditis caused by PVB19 has distinct features. PVB19 virus enters endothelial cells of intramyocardial blood vessels via blood group P-antigen and triggers a proinflammatory cytokine release after cell entry. Sustained inflammation and endothelial dysfunction, especially in the setting of viral persistence, may lead to myocyte necrosis. Although the detection of PVB19 genomes are increasingly common, more clarity is needed on differentiation of incidental viral replication versus pathogenicity of the virus (see Diagnosis section below).

Finally, data from mice models of myocarditis indicate that there may be a genetic susceptibility to the autoimmune process leading to myocarditis, wherein certain genetic variants are more prone to develop myocarditis, whereas other variants may confer resistance.

**Diagnosis**

Myocarditis is typically diagnosed using histopathologic criteria of endomyocardial biopsy samples. In the 1980s, the Dallas criteria for diagnosis were established. The Dallas criteria require an inflammatory infiltrate and evidence of myocyte necrosis not caused by an ischemic event. Borderline myocarditis is defined by less intense inflammatory infiltration and no evidence of myocyte necrosis. A major challenge
in the diagnosis of myocarditis relates to the poor sensitivity of the Dallas criteria. The sensitivity of RV biopsy is poor because of sampling error, which may be partly because of frequent predilection for involvement of the LV lateral free wall, based on cardiac magnetic resonance imaging (CMRI) studies (Figure 2). The use of LV biopsies increases the diagnostic yield, but LV biopsies are not commonly performed. In addition, interobserver agreement from pathologists on whether samples fulfill the Dallas criteria is low. Several efforts have been made to overcome the sampling error and subjectivity of biopsy criteria. First, immunohistochemistry criteria, including the number of leukocytes per square millimeter and measuring the upregulation and induction of major histocompatibility complex I and II antigens and intracellular adhesion molecule-1 from EMB samples can be diagnostic, with the latter a more uniform and less patchy process. More recently, studies have used molecular tools to enhance the diagnostic yield. In this regard, Heidecker et al showed that the use of molecular signatures from one EMB specimen is highly accurate for the diagnosis of lymphocytic myocarditis. Future studies using this approach are needed.

Additionally, the use of polymerase chain reaction (PCR) to detect viral genomes from EMB samples may be additive for diagnosis, although the sensitivity of this approach is not well established and its significance in the absence of inflammation is unclear. Evidence suggests that ongoing viral replication has negative prognostic implications. For example, patients with virus-positive myocarditis whose virus clears on subsequent biopsy are more likely to have improved LV ejection fraction compared with patients who have persistent viral replication. One retrospective trial shows that patients who are virus positive are less likely to respond to immunosuppression compared with patients who do not exhibit viral replication. Although the findings of these studies included patients with PVB19 and remained true in these patients, other studies indicate that PVB19 infection is often an incidental finding and does not play a role in the development of myocarditis. The evidence is complicated by the potential for latent low-level PVB19 viral replication, the various patient populations, timing of specimen collection, and detection techniques among the studies to date. However, myocarditis is more likely to occur in the presence of higher viral loads of PVB19, with a cutoff of 500 genome equivalents per microgram in one study. The European Society of Cardiology expert consensus group on myocardial diseases recommends EMB, including samples to analyze viral PCR and immunohistochemistry, for all patients with clinically suspected myocarditis. In a joint statement by the American Heart Association, American College of Cardiology, and European Society of Cardiology, the use of EMB was recommended based on particular clinical scenarios because the diagnosis is often not known until after EMB performed. The class I indications are for recent onset heart failure (ie, <3 months) with hemodynamic compromise, ventricular arrhythmias, high-degree atrioventricular block, or failure to respond to usual care. The cardiomyopathies that may meet these class I indications include giant cell myocarditis (GCM), fulminant lymphocytic myocarditis, and cardiac sarcoidosis (CS).

Additionally, the use of electrograms to perform targeted biopsies in areas of low amplitude has promise to enhance diagnostic yield of biopsies. New imaging modalities such as CMRI may also enhance detection of myocarditis. Consensus CMRI criteria have been established, with high specificity for inflammation and modest sensitivity (lesser in patients with <1 week onset of myocarditis), such that a negative study should not discourage further testing such as EMB if there is high clinical suspicion. CMRI is limited in that it cannot characterize myocarditis types. Finally, additional clinical characteristics such as presenting symptoms, electrocardiogram, and biomarker (ie, troponin) elevation have an additive but limited and nonspecific role in diagnosis.

Safety of EMB: EMB of the RV, performed via the femoral or jugular veins, has a low complication rate. Older series using the Caves-Schultz biopom, more rigid and with larger forceps than contemporary biopsy forceps, had an overall low rate of cardiac perforation (<1%) but 2 deaths out of 546 patients because of perforation. Recent studies of thousands of patients in aggregate, using smaller disposable forceps, have a similarly low rate of perforations (<1%) and no deaths. Other complications may include conduction abnormalities (more common via femoral approach 3% to 4% versus <1% via jugular approach), carotid puncture, and tricuspid valve damage (more common in patients undergoing repeated biopsies for heart transplant rejection surveillance). LV biopsies, although not widely performed, have a comparable safety profile to RV biopsies but differ in that there are fewer perforations, more access site hematomas, and have a rate of transient ischemic attacks of 0.2%.

**Treatment**

The treatment of lymphocytic myocarditis is, presently, mostly undifferentiated from that of the standard medical therapy for other nonischemic DCM. However, there are some key exceptions (Table 1). Patients with fulminant myocarditis, characterized by abrupt onset, profound hemodynamic compromise,
and extensive inflammation often need to be supported with intravenous inotropes or vasopressors and mechanical circulatory support.\textsuperscript{17,50} The prognosis for those that survive the initial course is excellent, with most survivors recovering fully.\textsuperscript{51} The role of immunosuppression for myocarditis is controversial.

The Dallas criteria were used for inclusion in the Myocarditis Treatment Trial, a highly influential trial showing no benefit of immunosuppression versus placebo.\textsuperscript{33} The use of immunosuppression as a general strategy is not helpful,\textsuperscript{33} but there may be a subset of patients for whom it is beneficial. For example,

### Table 1. Summary of Diagnostic Methods and Treatment Modalities for Various Types of Inflammatory Cardiomyopathy

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DIAGNOSIS</th>
<th>SPECIFIC TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic Viral Myocarditis</td>
<td>Biopsy: Dallas criteria; IHC criteria; (leukocytes/mm², MHC I and II) ? Viral PCR CMRI: “Lake Louise” criteria: 2 or more positive: Sens. 67%, Spec. 91%,</td>
<td>Standard HF therapy IV inotropes or vasopressors and MCS for fulminant. Immunosuppression e.g. (prednisone and azathioprine) can be considered for chronic viral and increased HLA expression.</td>
</tr>
<tr>
<td>HIV Cardiomyopathy</td>
<td>Diagnosis is Clinical: HIV+ plus Decreased EF and/or LV Dilation • If CD4&lt;200,cells/mL, consider OI such as toxoplasmosis or Cryptococcus • CAD should be considered Biopsy not routinely indicated CMRI findings: fibrosis, early gadolinium enhancement, myocardial edema</td>
<td>Standard HF therapy Scarce data HAART therapy preventive</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td>Clinical/Serology: CTD-specific diagnostic criteria plus evidence of cardiomyopathy Biopsy: monocyte infiltration with or without fibrosis • SLE: IMF; immune complexes and complement deposition in myocardial vasculature CMRI: Subclinical myocarditis (i.e. delayed GE, increased T2-weighted edema, early GE) fairly common in RA and SSc</td>
<td>Standard HF therapy Corticosteroids +/- azathioprine, cyclophosphamide, mycophenolate, IVIG, rituximab, plasmapheresis, and other immunosuppressive therapies</td>
</tr>
<tr>
<td>Giant cell Myocarditis</td>
<td>Biopsy: Characteristic multinucleated giant cells, serpiginous necrosis, mixed inflammatory infiltrate of lymphocytes, histiocytes, and frequently eosinophils (If clinical suspicion high, consider repeat EMB: Increases sensitivity from 68 to 93%)</td>
<td>Muromonab CD3 + long-term cyclosporine + steroids. Anti-thymocyte globulin + long-term corticosteroids. Multi-drug IS: azathioprine, cyclosporine, and prednisone. MCS and OHT</td>
</tr>
<tr>
<td>Cardiac Sarcoidosis</td>
<td>Biopsy: Poor sensitivity (25%) non-caseating granulomas with infiltration of myocardium Imaging (can be suggestive but not definitive for diagnosis): • CMRI: high NPV, LGE • FDG-PET (inferior sensitivity compared to CMRI) • Gallium scan Clinical and/or Histological: Japanese Ministry of Health and Welfare Criteria</td>
<td>Standard HF therapy Steroids Additional IS: methotrexate, azathioprine, etc. AAD and low threshold for ICD</td>
</tr>
<tr>
<td>Chagas</td>
<td>Acute Chagas CMP • PCR (also useful to detect reactivation) or positive blood smear Chronic Chagas CMP • Serology: ELISA, IF to detect IgG ab against T. cruzi (diagnosis requires 2 separate serological tests) • PCR poorly sensitive</td>
<td>Standard HF therapy Anti-trypanosomal Rx for acute forms and indeterminate form. No significant clinical benefit vs placebo for chronic Chagas AAD and low threshold for PPM/ICD</td>
</tr>
<tr>
<td>Hypersensitivity Myocarditis</td>
<td>Clinical: Peripheral eosinophilia and clinical signs of heart failure Biopsy: IIA recommendation for DCM with allergic reaction or eosinophilia Shows myocarditis with eosinophilic infiltrate</td>
<td>Identification and cessation of inciting agents. Corticosteroids may be beneficial.</td>
</tr>
<tr>
<td>Löffler’s Endocarditis</td>
<td>Occurs in temperate climates Lab: Eosinophil counts &gt; 1500 per mm³ for at least 6 months. Echo: thickening of the posteroasal portion of LV wall, substantial impairment in the motion of posterior leaflet of the MV, apex may be obliterated by thrombus. Biatrial enlargement, preserved systolic function. Biopsy not routinely indicated</td>
<td>Corticosteroids and hydroxyurea- favorable outcome. Interferon as adjunctive therapy for refractory. Anticoagulation for thrombotic burden. Novel monoclonal antibodies against IL-5 safe and successful in reducing eosinophilia, but modest clinical benefits.</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>Occurs in tropical or subtropical climates Lab: Unclear link to eosinophilia Diagnosis made clinically and by imaging findings • Clinical; signs of right and/or left heart failure • Echo: fibrotic obliteration of apex Biopsy not routinely indicated</td>
<td>Surgical resection with AV valve replacement.</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs; CAD, coronary artery disease; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; GE, gadolinium enhancement; HAART, highly active antiretroviral therapy; HF, heart failure; IF, immunofluorescence; IHC, immunohistochemistry; IS, immunosuppression; MCS, mechanical circulatory support; NPV, negative predictive value; OHT, orthotopic heart transplant; OI, opportunistic infection; RA, rheumatoid arthritis; Rx, therapy; SLE, systemic lupus erythematosus; and SSc, systemic sclerosis.
patients with chronic myocarditis (ie, >6 months) who have PCR negative for virus at 6 months and patients with increased human leukocyte antigen expression may benefit from immunosuppressive agents such as prednisone and azathioprine. A large trial of intravenous immunoglobulin for patients with recent-onset DCM did not perform better than placebo, but this included only a minority (<12%) of patients meeting the Dallas criteria. Smaller studies have shown mixed benefits of the use of intravenous immunoglobulin for myocarditis, with some positive signals in pediatric populations. Finally, the use of interferon-β for patients with adenosivirus or enterovirus results in viral clearance and may have benefit for patients with chronic myocarditis. Given the sparse data, more randomized controlled trials are clearly needed to evaluate immunosuppressive, immune-modulating, or antiviral therapies. Hopefully, coupling sophisticated diagnostic techniques to more individualized therapeutic approaches will yield enhanced success for the management of myocarditis in the future.

**HIV Cardiomyopathy**

Viral infection with HIV leads to some unique cardiac issues. The prevalence of systolic dysfunction in patients with HIV on highly active antiretroviral therapy is ≈8.3% in Western countries and higher in poorer countries in which highly active antiretroviral therapy is less available. Potential causes of cardiomyopathy include coronary artery disease, direct viral toxicity, autoimmune response, HIV medications, nutritional deficiencies, and myocarditis because of other viruses or opportunistic infections such as toxoplasmosis or cryptococcosis. Cardiotropic viruses, frequently more than one, are more frequently present in HIV+ patients compared with patients with idiopathic DCM, although a causative role has not been proven. It is not known whether HIV is directly toxic to the myocardium, and HIV may require coinfection with other viruses to enter myocytes. The virus is known to infect cardiac macrophages and dendritic cells and trigger inflammatory responses. The role of inflammation in HIV cardiomyopathy is supported by CMRI studies that show a high incidence of findings suggestive of inflammation (ie, fibrosis, early gadolinium enhancement, myocardial edema) in asymptomatic HIV patients on highly active antiretroviral therapy. Autopsies of children who died from noncardiac conditions of HIV show a mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and polymorph nuclear cells, with distortion of the myocyte architecture. In this study and also in studies of EMBs of patients with HIV cardiomyopathy, there was increased expression of major histocompatibility class I antigen and increased numbers of infiltrating CD8+ T lymphocytes. Cardiac autoantibodies and proinflammatory cytokines TNF-α, IL-1, and IL-6 are all increased in HIV+ patients with cardiomyopathy. TNF-α and other cytokines lead to increased inducible nitric oxide synthase expression, inversely proportional to CD4 count, causing myocyte apoptosis. Thus, there is robust evidence of inflammation in patients with HIV cardiomyopathy. However, there is scarce data on therapies targeting the inflammatory pathways. Highly active antiretroviral therapy has led to a decline in the incidence of cardiomyopathy in HIV+ patients, although its efficacy in reversing established HIV cardiomyopathy is not proven.

**Autoimmune Myocarditis Associated With Connective Tissue Disorders**

Lymphocytic myocarditis is also associated with various CTDs including systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis (RA), dermatomyositis, and polymyositis. Approximately 10% of patients with SLE will have clinical myocarditis, and African American patients with SLE are at increased risk. Clinically apparent myocarditis associated with RA is less common compared with SLE, and it is either interstitial or granulomatous. However, CMRI studies have discovered that subclinical myocarditis in RA and systemic sclerosis is common, with small series showing approximately half of patients with delayed gadolinium enhancement.

**Pathophysiology**

Immunofluorescence of patients with lupus myocarditis shows immune complexes and complement deposition in the myocardial vasculature, and EM shows a monocyte infiltration with or without fibrosis typical of lymphocytic myocarditis. Myocardial disease in patients with systemic sclerosis has been suggested to be because of recurrent vasospasm of small vessels with resultant focal ischemia, but recent data incorporating EMB and showing a high frequency of lymphocytic myocarditis in patients challenge the vasospasm paradigm as the predominant cause of cardiomyopathy. Rheumatoid arthritis is characterized by enzymatic conversion of arginine to citrulline (ie, citrullination) and a subsequent autoimmune response manifest by the production of anticitrullinated protein antibodies. Interestingly, citrullination in myocardial interstitium is much greater in autopsy samples from patients with RA compared with patients with scleroderma or controls. RA patients with high levels of anticitrullinated protein antibodies have a greater LV mass index on CMRI compared with patients with low levels, suggesting a possible pathophysiological connection between RA and the development and cardiomyopathy.

In addition to myocarditis, there are other processes that can lead to systolic dysfunction in patients with CTDs, including coronary artery disease, valvular disease (ie, Libman–Sacks endocarditis in SLE), and medications. Hydroxychloroquine, a disease-modifying agent commonly used to treat SLE and RA, can cause cardiotoxicity, especially with prolonged and cumulative use. It may cause a restrictive cardiomyopathy with increased ventricular thickness with or without LV systolic dysfunction, and sometimes requires EMB to differentiate from myocarditis. Histological findings include characteristic myocyte vacuolization, glycogen deposition in cytoplasm, and electron microscopy shows lamellar lysosomal inclusions and curvilinear bodies. Patient with SLE are at increased risk for coronary artery disease, because of a variety of factors including inflammation and immune complex deposition, glucocorticoid use, and in some cases associated antiphospholipid syndrome.

**Treatment**

Although lupus myocarditis patients have similar outcomes as idiopathic DCM patients, patients with myocarditis associated...
with systemic sclerosis or undifferentiated CTD have worse outcomes. Standard treatment of myocarditis associated with CTD typically consists of corticosteroid pulses but for refractory cases other treatment options may include azathioprine, cyclophosphamide, mycophenolate, intravenous immunoglobulin, rituximab, and plasmapheresis. The use of anti–tumor necrosis factor agents should be avoided in patients with symptomatic heart failure.

**Giant Cell Myocarditis**

GCM, first described in 1905, is a rare and severe inflammatory disease of the heart. Before the establishment of an international registry in 1997, only case reports and case series existed in the literature to characterize the disease. Because the disease is characterized by a sudden onset and rapid deterioration, before the advent of heart transplantation and the development of sophisticated immunosuppressive medications, most cases were diagnosed at autopsy. Patients who develop GCM are typically young (mean age 40 years) and have a history of autoimmune disorders. Most patients present with acute heart failure, and 50% will have refractory ventricular tachycardia during the course of the disease. Patients may also present with varying degrees of heart block. Median survival without transplant or immunosuppression is ≈3 months.

Animal models and human studies have provided evidence that GCM is an autoimmune disorder mediated largely by T-cell activity. First, immunization of rats with cardiac myosin in an experimental model leads to the development of GCM. In addition, gene expression analysis of patients with GCM show increased immune response, particularly an upregulation of chemokines involved in activation of Th1 cells. As opposed to lymphocytic myocarditis, there is not a significant presence of cardiac autoantibodies in patients with GCM, suggesting an autoimmune response dominated by T cells rather than B cells. Response to T-cell–directed immunosuppression also supports this theory. In addition, animal models implicate a possible role of Treg cells in the development of GCM. Mice that are depleted of Foxp3-expressing CD4 cells (a marker specific for Treg cells) develop an autoimmune myocarditis characterized by multinucleated giant cells.

The diagnosis of GCM is histological and ideally made by endomyocardial biopsy or from an explanted heart. Histological findings are characterized by serpiginous necrosis, characteristic multinucleated giant cells, and a mixed inflammatory infiltrate of lymphocytes, histiocytes, and frequently eosinophils. If clinical suspicion is high and initial EMB is negative, repeat EMB should be considered as this increases the diagnostic yield (increased sensitivity from 68% to 93% in one study).

Immunosuppression with steroids alone offers no survival advantage. However, steroids in combination with additional immunosuppression improves survival although the optimal regimen is unknown. The short-term use of muromonab-CD3, a monoclonal antibody that binds to the T-cell receptor–CD3 complex on circulating T cells, followed by long-term cyclosporine and steroids leads to high 1-year survival. The use of rabbit antithymocyte globulin plus corticosteroids also has had success in a small case series of patients with GCM. The use of multidrug immunosuppression, consisting predominantly of azathioprine, cyclosporine, and prednisone without T-cell depletion, also improves survival compared with historical controls, with 5-year transplant-free survival of 52%. However, this survival is inferior to long-term survival with heart transplantation, and more than half of surviving patients still experienced ongoing ventricular arrhythmias. Finally, there is a case report of remission with total lymphoid irradiation.

Patients with GCM are more likely to need mechanical circulatory support, often biventricular, as a bridge to transplantation compared with patients with DCM.

GCM may recur in ≈26% of patients post-transplant at various time periods after transplant, and this risk should be considered when planning surveillance biopsy schedules in this unique population. Data in small series is mixed regarding post-transplant outcomes, but recent analysis of the United Network of Organ Sharing database shows similar outcomes post-transplant compared with patients with idiopathic DCM.

**Sarcoidosis**

Sarcoidosis is discussed extensively by Muchtar et al, in a separate article in this Compendium. Therefore, only the role of inflammation in the pathogenesis of sarcoidosis is discussed here. Sarcoidosis is considered an inflammatory disorder involving multiple organ systems, including the eyes, skin, lungs, lymphatic system, and heart.

Although sarcoidosis is clearly an inflammatory disease, the pathogenesis and inciting events are incompletely understood. There is a genetic predisposition, reflected in an increased risk of developing the disease among relatives of patients with sarcoidosis. Gene studies implicate the immune system as alleles of the human leukocyte antigen-DRB 1 locus are more common in patients with sarcoidosis. In addition, environmental exposures have also been linked to the development of the disease as have many micro-organisms, albeit with less robust data.

Histologically, it manifests with an accumulation of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas. The granuloma consists of tightly packed follicle made up of lymphocytes (especially CD4+ T cells), giant cells, and epithelioid cells surrounded by a rim of fibroblasts and lymphocytes (including B cells and both CD4+ and CD8+ T cells). TH1 activation occurs early in the disease process and interacts with antigen-presenting cells to form the granulomas, followed by TH2-mediated fibrosis. There is increased gene expression of T helper 1 cell cytokines in the myocardium of sarcoid patients. Paradoxically, despite the activation of the immune system, sarcoidosis is also manifest by peripheral T-cell anergy that is at least in part mediated by the expansion of T regulatory cells.

Similar to lymphocytic myocarditis, because of the patchy nature of disease, advanced analysis of biopsy samples holds promise for enhanced diagnosis. For example, EMB samples from patients with cardiac sarcoid are more likely to contain high numbers of CD209+ dendritic cells and CD68+
macrophages and less likely to have CD 163+M2 macrophages compared with nonischemic cardiomyopathy controls.97 In addition, CS has a gene expression profile distinct from those of GCM or lymphocytic myocarditis, although there is not currently a specific gene expression profile that can be used clinically for the diagnosis of CS.96,98

There has not been a randomized placebo-controlled trial of corticosteroids in CS. Nevertheless, retrospective and observational studies indicate that the use of steroids improves outcomes,99 can reverse conduction abnormalities,100 and can prevent LV remodeling.101 Optimal dose is unknown. Small case series and extrapolation from the treatment of pulmonary sarcoidosis has led to the use of steroid-sparing agents such as methotrexate and azathioprine.102 Case reports have suggested the possible benefit of infliximab, an anti–tumor necrosis factor-α agent,103 although this agent is contraindicated in patients with advanced heart failure. To minimize the long-term adverse effects of steroids and to optimize treatment options, more studies are needed on immunosuppression options for the treatment of sarcoidosis.

Chagas
Chagas disease, or American trypanosomiasis, is the most common cause of nonischemic cardiomyopathy in Latin America. The global prevalence of Chagas disease is ≈8 to 12 million, with the highest prevalence in Bolivia (7%) and greatest number of cases in Brazil.104 With migration from Latin American countries to the United States, Chagas disease is becoming more common, especially in states with high migration from endemic areas. For example, in New York City, among patients with DCM who lived in endemic areas for at least a year, 13% of patients tested positive for Chagas.105

Chagas disease is caused by infection with the protozoa Trypanosoma cruzi, most often transmitted via Triatominae insect vectors, but also occurring via blood transfusion, or Trypanosoma cruzi, most often transmitted via Triatominae. Hypersensitivity Myocarditis

Eosinophilic myocarditis is a broad term to describe inflammatory cardiomyopathies of various pathogeneses associated with eosinophils. Eosinophilic myocarditis may present initially and in some cases may advance to endomyocardial fibrosis. Eosinophils contain cytoplasmic granules that release cytotoxic proteins on activation from immunogenic stimuli, potentially leading to free radical formation and subsequent apoptosis or necrosis.

Endomyocardial disease is a term used to describe 2 major variants of restrictive cardiomyopathy with overlapping features and potential eosinophilic involvement yet are likely 2 distinct diseases. Both variants manifest pathologically with aggressive endocardial scarring that obliterates the ventricular apices and subvalvular regions. Löeffler endocarditis (or hypereosinophilic syndrome [HES]) occurs in temperate climates, is highly aggressive, and has a clear association with hypereosinophilia. Endomyocardial fibrosis occurs in tropical or subtropical climates, affects younger patients, and is only variably associated with eosinophilia.

Hypersensitivity Myocarditis
Hypersensitivity myocarditis, a form of eosinophilic myocarditis, is typically drug or vaccine related. It is rare, accounting for <1% of unexplained cardiomyopathies.47 Higher incidences have been described in explanted hearts of patients undergoing transplant, but this is likely because of a high use of dobutamine to bridge patients to transplant, and multiple reports of dobutamine-associated eosinophilic myocarditis have been described.12,113 There are numerous drugs that have been associated with hypersensitivity myocarditis (Figure 1), and the disorder is usually temporally related to the inciting
drug. However, in rare cases, myocarditis can develop in patients years after initiation of the responsible drug. Cardiac biopsy has a reasonably high yield in patients suspected of the disease, showing myocarditis with a eosinophilic infiltrate, but may be subject to sampling error. Heart failure associated with a suspected allergic reaction or eosinophilia is given a class IIA recommendation for EMB by expert consensus. Peripheral eosinophilia plus cardiac signs should raise suspicion, but it may be absent in early stages of disease. Treatment should focus on identification and cessation of inciting agent, if possible. Corticosteroids may be beneficial.

The smallpox vaccine also may cause myopericarditis, with an eosinophilic and lymphocytic infiltrate. A large prospective study found that >10% of patients will have cardiac symptoms (ie, chest pain, palpitations, dyspnea) within 30 days of vaccination, 0.4% will be diagnosed with clinical myocarditis and pericarditis, and 2% to 3% will have subclinical myocarditis as defined by cardiac troponin elevation.

Löffler Endocarditis
Hypereosinophilia associated with Löffler endocarditis usually is characterized by eosinophil counts exceeding 1500 per mm³ for at least 6 months. The eosinophilia may be secondary to leukemia or other neoplastic disorders or to reactive disorders such as parasite infection, allergies, granulomatous syndromes, or hypersensitivity. In addition, patients with Churg–Strauss syndrome, characterized by asthma or allergic rhinitis and a necrotizing vasculitis, often have cardiac involvement. Most cases, however, are idiopathic. HES is rare, with an unknown exact prevalence.

Patients with HES exhibit weight loss, fever, cough, rash, and congestive heart failure. More than half of patients progress to have overt heart failure symptoms, and mitral regurgitation is common. Systemic emboli occur frequently—resulting in neurological and renal sequelae. Death results from heart failure associated with renal, hepatic, or pulmonary involvement. In addition, the skin and gastrointestinal tract are commonly involved. Both chambers of the heart are involved and manifest with endocardial thickening of the inflow regions and ventricular apices. Histologically there are variable degrees of eosinophilic myocarditis of the myocardium and subendocardium, thrombosis and inflammation of small intramural coronary vessels, mural thrombosis containing eosinophils, and endocardial fibrotic thickening several millimeters thick.

Autopsy studies give insight into the pathophysiology and progression of endomyocardial disease. Hypereosinophilia, regardless of cause, leads to necrosis, intense myocarditis, and arteritis (ie, Löffler endocarditis). Patients with HES have degranulated eosinophils in their peripheral blood, supporting the theory that these granules are cardiotoxic and trigger necrosis. The eosinophils may also directly attack endomyocardial tissue. The necrotic phase lasts for a period of months and is then followed by a thrombotic stage, in which nonspecific thickening of the myocardium with a layer of thrombus replaces the inflammatory portion of myocardium. The final phase is characterized by endomyocardial fibrosis.

Echocardiogram often shows regional thickening of the posterobasal portion of the LV wall, with substantial impairment in the motion of the posterior leaflet of the mitral valve, and the apex may be obliterated by thrombus. As is typical for restrictive cardiomyopathy, biatrial enlargement is common and systolic function is often preserved. Contrast echocardiography and CMRI are also useful for diagnosis and to define the thrombotic burden. Endomyocardial biopsy can provide diagnostic confirmation, but is not required nor is it always positive.

There is a role for both medical and surgical therapy in improving quality and quantity of life in patients with Löffler endocarditis. There are several reports demonstrating a favorable outcome with the use of corticosteroids and cytotoxic drugs such as hydroxyurea. Interferon may also be beneficial as adjunctive therapy in refractory patients. Antiocoagulation also can reduce the thrombotic burden.

Novel targeted therapies have been developed to target eosinophilic-associated disorders, including for the treatment for eosinophilic myocarditis and HES. IL-5, produced by TH2 helper cells, is the major cytokine responsible for eosinophil differentiation, survival, and activation; thus, it is a natural target for molecular therapies. Indeed, two monoclonal antibodies (mepolizumab and reslizumab) that bind IL-5 have been developed and tested in various eosinophil-associated disorders and have shown to be safe and successful in reducing eosinophilia but have only had modest clinical benefits. Mepolizumab was tested for patients with HES and met the primary clinical end point of steroid reduction, but it is not FDA-approved for this indication. In addition, many biologicals targeting eosinophilic surface receptors and soluble mediators associated with eosinophil inflammation are under investigation.

Endomyocardial Fibrosis
Endomyocardial fibrosis (or Davies disease) is a disorder found typically in tropical and subtropical Africa, and is the most common form of restrictive cardiomyopathy in the world. A recent population based study in rural Mozambique revealed a 19.8% prevalence of the disorder in the population. It is increasingly recognized in other regions within 15 degrees of the equator (eg, India, Brazil). It is most common in children and young adults. Although there is some evidence to suggest a possible link between endomyocardial fibrosis and eosinophilia, the link is not as clear or consistent as it is for HES. Supportive evidence for additional theories include genetic, autoimmune as anti-myosin antibodies have been recently discovered in endomyocardial fibrosis patients, and high dietary cerium content.

Histologically, there is a thick layer of collagen overlaying loosely arranged connective tissue. In addition, there are fibrous and granular septations extending into the underlying myocardial tissue. Myocyte hypertrophy and interstitial edema are common yet cellular infiltration is not. Examination of intramural coronary arteries may show involvement with medial degeneration, the deposition of fibrin, and fibrosis. Endomyocardial fibrosis affects the RV, LV, or both. The hallmark feature of the disorder is fibrotic obliteration of the apex of the affected ventricle(s). Endocardial calcific deposits can be present involving diffuse areas of the ventricle. The fibrotic tissue often creates a nidus for thrombus formation, which can
be extensive. Atrial thrombi also occur. The process usually does not involve the epicardium and the coronary artery obstruction is distinctly uncommon. Diagnosis is typically made by clinical and echocardiography findings.\textsuperscript{121}

Clinical manifestations of heart failure depends on which ventricle(s) is involved. Atrioventricular regurgitation is common. Ascites, particularly in the absence of peripheral edema, is common. Pleural and pericardial effusions are also common. Atrial fibrillation is frequently present as the disease progresses and portends a worse prognosis.\textsuperscript{129} Endomyocardial fibrosis is typically a relentless and progressive process although some patients have periods of stability. Modes of death include progressive heart failure, infection, infarction, sudden cardiac death, and complications of surgery.

The medical management of endomyocardial fibrosis remains challenging. One third to one half of patients with advanced disease die within 2-years. Once endomyocardial fibrosis progresses to severe endocardial fibrosis, surgical resection with atrioventricular valve replacement is the treatment of choice. Although operative mortality is high, between 15 and 25\%, and fibrosis may recur, more than half of patients may achieve excellent long-term survival.\textsuperscript{130}

**Inflammation in DCM**

Inflammation is an adaptive response to cardiac injury, but the role of an excess or prolonged inflammatory response has been well established as maladaptive and crucial to the pathophysiology of heart failure of all pathogeneses. Evidence for cell-mediated immunity includes involvement of proinflammatory cytokines and lymphocytic infiltration on biopsies in almost half of patients with idiopathic DCM.\textsuperscript{130} The pathological role for several proinflammatory cytokines in heart failure have led to several trials of therapies directed against these cytokines. TNF-\(\alpha\) is the quintessential example of one such cytokine for which a wealth of evidence supports its role in heart failure, but greatly anticipated clinical trials of anti-TNF\(\alpha\) but not to the IgG3 subclass or to patients with \(\beta\)-1 autoantibodies altogether. As most patients in this study were on \(\beta\)-blocker therapy, it is difficult to account for the interactions of these drugs on these particular findings. Furthermore, the potential benefit of higher levels of IgG3 seem to be contradictory to small trials of immunoadsorption.

In addition to the cellular immune response exemplified by TNF-\(\alpha\), the humoral immune response is also active in DCM. For example, autoantibodies against myocardial \(\beta\)-1 adrenergic receptors are present in 26\% to 60\% of patients with idiopathic DCM (versus 10\% to 13\% of ischemic cardiomyopathy patients), and they are present in >80\% of patients with end-stage heart failure.\textsuperscript{134} IgG and the IgG3 subclass (which is a potent activator of complement) are deposited in 71\% and 48\%, respectively, of hearts in patients with end-stage heart failure of diverse pathogeneses.\textsuperscript{1} Although the presence of autoantibodies against \(\beta\)-1 adrenergic receptors typically has negative implications, recent data showed that antibodies against the IgG3 subclass of \(\beta\)-1 receptors antibodies are associated with improvements in LV ejection fraction and clinical outcomes compared with patients with antibodies to \(\beta\)-1 receptors but not to the IgG3 subclass or to patients without \(\beta\)-1 autoantibodies altogether. As most patients in this study were on \(\beta\)-blocker therapy, it is difficult to account for the interactions of these drugs on these particular findings. Furthermore, the potential benefit of higher levels of IgG3 seem to be contradictory to small trials of immunoadsorption that show enhanced benefit when modified to more specifically target IgG3.\textsuperscript{135} In addition to \(\beta\)-1 autoantibodies, there is also a high prevalence of other autoantibodies, ie, \(\alpha\)-myosin and cardiac troponin-I, in patients with DCM.

Animal models of heart failure also elucidate the role of the humoral immune system in the pathophysiology of heart failure. For example, a mouse model of nonischemic cardiomyopathy was applied to severe combined immunodeficient, B-cell depleted, T cell deficient, and control mice. Only the severe combined immunodeficient and B-cell depleted mice were protected from cardiomyopathy and only upon B-cell reconstitution did the mice developed cardiomyopathy. The cardiomyopathy was also manifest by increased inflammatory cytokine release and IgG3 deposition, which was highly associated with apoptosis. Thus, this data suggests that the development of cardiomyopathy may require B-cell activation, with implications for future trials of therapies to prevent B-cell activation.\textsuperscript{136}

It should also be noted that there is evidence for inflammation as a possible pathogenesis in peripartum cardiomyopathy in addition to genetic and hormonal evidence. Patients with peripartum cardiomyopathy are more likely to have viral genomes present\textsuperscript{137} and have cardiac autoantibodies (ie, anti-myosin and anti-troponin).\textsuperscript{138}

**Future Directions**

Inflammatory cardiomyopathies are a diverse group of disorders, and although much knowledge has been gained in the past few decades, there remains a staggering amount that is unknown. Lymphocytic viral myocarditis is arguably the most studied type, but the exact pathophysiology is not completely known and is largely limited to animal models. Further insight is needed regarding the interaction of genes and environmental exposures in causing pathological inflammation (Figure 3). Furthermore, studies of specific treatment strategies are limited.
by such factors as imperfect gold standards, small number of patients studied, variable timing and types of treatments, and few randomized placebo-controlled studies. More trials of autoimmune therapies targeted at specific populations (ie, virus negative chronic lymphocytic myocarditis) are underway (ie, NCT01877746 comparing 2 different dosing schedules of azathioprine and prednisone versus placebo) and will be informative (Table 2). More therapeutic trials are needed not only in viral myocarditis, perhaps with more refined entry criteria to ensure targeting those with active inflammation, but they are also needed in other inflammatory cardiomyopathies such as sarcoidosis, autoimmune myocarditis associated with CTDs, and eosinophilic myocarditis.

Further advances in molecular biological diagnostic techniques, particularly in virology and gene expression, are foreseeable. Initial studies using gene expression profiles to

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CMP indicates cardiomyopathy; CMRI, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; HF, heart failure; IHC, immunohistochemistry criteria; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; and PVB19, parvovirus B10.

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Table 2. Summary of Ongoing Therapeutic Trials for Myocarditis, According to Results of a Search for Myocarditis or Inflammatory Cardiomyopathy on the United States National Institutes of Health registry ClinicalTrials.gov
distinguish myocarditis from idiopathic DCM and CS from GCM have shown great promise.\textsuperscript{36,98} If further studies corroborate these findings, then one can use such molecular biomarkers to refine the entry criteria for therapeutic trials. In addition, the relative expression of particular genes may also provide mechanistic insights into the pathophysiology of inflammatory cardiomyopathies and provide targets for RNA interference. While standard viral PCR for the diagnosis of myocarditis typically analyzes fewer than ten known viruses, a microarray approach to detect hundreds of potential viruses simultaneously (ie, the ViroChip)\textsuperscript{139} could be transformative if applied to endomyocardial tissue. The use of such technology could even lead to discoveries of new viruses, such as the Saffold virus, a cardiovirus of the Picornaviridae family that has recently been discovered and implicated in clinical myocarditis.\textsuperscript{140} In addition, more data on the role of the virus (especially PVB19) in the pathophysiology of viral myocarditis is needed. More insight may be gained from an ongoing trial of intravenous immunoglobulin in patients with > 200 copies/μg DNA of PVB19 (NCT 00892112). Although early trials showed potential for antiviral therapy, the benefit of such therapies are not established. Finally, vaccinations for the most common pathogens that cause infectious myocarditis could be considered for prevention of myocarditis.

Recent paradigm shifts have changed our understanding of immunologic concepts. For example, in the past few years, resident cardiac macrophages that were established during embryonic development and without derivation from monocytes have been discovered.\textsuperscript{141} Greater understanding of these and other cell types could lead to improvements in regenerative therapies, which hold great promise for improving cardiomyopathies of all pathogeneses. Recently, mesenchymal cells (especially allogeneic) delivered transendocardially to patients with ischemic and nonischemic heart failure showed favorable anti-inflammatory benefits, including reduction in TNF-α as well as reverse remodeling (Figure 4).\textsuperscript{142} More studies on the cardiac anti-inflammatory effects of mesenchymal stem cells are needed. Additionally, animal models have showed favorable effects of antagonizing IL-1 receptors in viral myocarditis; therapeutic trials in humans with acute myocarditis are underway to target this pathway with the drug Anakinra, an IL-1 antagonist used for the treatment of RA (NCT03018834).

Additionally, a tremendous amount has been learned about T-helper subsets and their various roles. One may envision an opportunity to target the proliferation of specific immune cell types (ie, Tregs) to harness the immune system’s capacity to self-regulate or to target cell types (ie, Th17) involved in the proinflammatory pathway. Nevertheless, much remains to be learned about the various functions of these subsets.

Recently, immune checkpoint inhibitors that have revolutionized the treatment of some cancers have been implicated as the cause of two fatal cases of fulminant myocarditis. Analysis of pharmaceutical databases reported that in patients on combination therapy with two such inhibitors, there is an incidence of myocarditis of 0.27%.\textsuperscript{143} As the use of therapies that harness the immune system’s ability to fight cancer is expected to surge, more data are needed on the mechanisms underlying myocarditis in these patients. Finally, the use of platforms to deliver nanoparticles also has great potential to deliver anti-inflammatory therapies locally while minimizing or eliminating systemic toxicities. Nanovectors have recently been shown to have the capacity to accumulate intracellularly in the failing myocardium,\textsuperscript{144} and this proof-of-concept should lead to more research in the field of heart failure.

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A Review of Common Causes of Myocarditis


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