Myocarditis*
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Abstract

Myocarditis is an uncommon, potentially life-threatening disease that presents with a wide range of symptoms in children and adults. Viral infection is the most common cause of myocarditis in developed countries, but other etiologies include bacterial and protozoal infections, toxins, drug reactions, autoimmune diseases, giant cell myocarditis, and sarcoidosis. Acute injury leads to myocyte damage, which in turn activates the innate and humoral immune system, leading to severe inflammation. In most patients, the immune reaction is eventually down-regulated and the myocardium recovers. In select cases, however, persistent myocardial inflammation leads to ongoing myocyte damage and relentless symptomatic heart failure or even death. The diagnosis is usually made based on clinical presentation and noninvasive imaging findings. Most patients respond well to standard heart failure therapy, although in severe cases, mechanical circulatory support or heart transplantation is indicated. Prognosis in acute myocarditis is generally good except in patients with giant cell myocarditis. Persistent, chronic myocarditis usually has a progressive course but may respond to immunosuppression. (Prog Cardiovasc Dis 2010;52:274-288)

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Myocarditis presents with a spectrum of symptoms ranging from mild dyspnea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy (DCM) with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated. The diagnosis can usually be made based on clinical presentation and noninvasive imaging findings, but endomyocardial biopsy (EMB) may be indicated in select cases. Treatment and prognosis vary according to etiology and may include mechanical cardiac assist devices or heart transplant for severe cases. The aim of this review was to provide a concise and practical approach to the evaluation and treatment of suspected myocarditis.

Definition

The Dallas criteria were proposed in 1986 to provide a histopathologic classification for the diagnosis of myocarditis. These criteria require that an inflammatory cellular infiltrate with or without associated myocyte necrosis be present on conventionally stained myocardial tissue sections. Although these criteria have been used for more than 20 years, they are limited by variability in expert interpretation, lack of prognostic value, discrepancy with other markers of viral infection and immune activation in the myocardium, and low sensitivity that is at least partly due to sampling error.1,2 Newer histologic criteria rely on cell-specific immunoperoxidase stains for surface antigens such as anti-CD3, anti-CD4, anti-CD20, anti-CD28, and antihuman leukocyte antigen.3,4 Recent research has shown that...
criteria based on this type of staining has greater sensitivity than the Dallas criteria and may have prognostic value.5

Although EMB has long been the gold standard for confirming the diagnosis of myocarditis, preliminary studies have shown that cardiac magnetic resonance imaging (MRI) has become an important tool for noninvasive assessment of patients with suspected myocarditis.6-8 Cardiac MRI diagnostic targets include functional and morphological abnormalities as well as tissue pathology as characteristic of myocardial inflammation. Given the lack of consensus regarding the role of EMB and the excellent prognosis of patients with mild acute DCM who have suspected myocarditis, a recent consensus statement recommends that EMB be reserved for patients who are likely to have specific myocardial disorders with unique prognoses and specific treatment recommendations.9

Incidence and natural history of myocarditis

The true incidence of myocarditis has been difficult to determine because clinical presentations vary widely, and EMB is rarely used due to perceived risks and lack of a widely accepted and sensitive histologic standard. Autopsy reports have revealed varying estimates of the incidence of myocarditis according to the population studied, with estimates ranging from 0.12% to 12%.10-14 The Myocarditis Treatment Trial reported the incidence of biopsy-documented myocarditis in patients with unexplained heart failure to be 9.6%.15 The observation that there is a high prevalence of viral genomes in patients with DCM16 and that viral genomes are more common in patients with chronic DCM than in patients with ischemic heart disease suggests that viral myocarditis may lead to a substantial disease burden in the community.

Most studies of acute myocarditis report a slight predominance of men,17-19 which may be partly mediated by sex hormones. In female mice, estrogenic hormones have been shown to protect against viremia and viral infectivity of cardiomyocytes,20 while also decreasing the potentially harmful myocardial inflammatory response.21 In contrast, testosterone has been shown to have a detrimental effect through inhibition of antiinflammatory responses in male mice.22

Young adults are most commonly affected. The mean age of patients with giant cell myocarditis (GCM) is 42 years,23 whereas the mean age of adult patients with other forms of myocarditis has been reported to range from 20 to 51 years.24,25 The consequences are sometimes devastating in this population, as acute myocarditis has been shown to be the cause of sudden death in up to 12% of cases in autopsy studies of patients less than 40 years of age,14,26-28 military recruits,28 and young athletes.29

Myocarditis is also an important cause of sudden death in children30-32 as well as childhood cardiomyopathy.33,34 The risk of death and heart transplantation persists up to 12 years after diagnosis of acute myocarditis in the pediatric population.35

Occasionally, myocarditis occurs concurrently with other cardiomyopathies and may adversely affect outcomes. For instance, mortality is higher in patients with cardiac amyloidosis if histologic evidence of myocarditis is present.36 Similarly, patients with hypertrophic cardiomyopathy deteriorate more quickly if myocarditis is present.37 Although myocarditis may mimic arrhythmogenic right ventricular cardiomyopathy (dysplasia) in clinical presentation and the presence and severity of structural and functional right ventricular abnormalities,38 the 2 diseases may also occur simultaneously.39

Clinical presentation

Adults

The clinical presentation of acute myocarditis in adults is highly variable, ranging from subclinical disease to fulminant heart failure. A viral prodrome including fever, rash, myalgias, arthralgias, fatigue, and respiratory or gastrointestinal symptoms frequently, but not always, precedes the onset of myocarditis by several days to a few weeks. Patients may present with chest pain, dyspnea, palpitations, fatigue, decreased exercise tolerance, or syncope. Chest pain in acute myocarditis may mimic typical angina and be associated with electrocardiographic changes, including ST-segment elevation. Rarely, chest pain associated with coronary artery vasospasm may occur in patients with myocarditis.40 Alternatively, chest pain may be more typical for pericarditis, suggesting pericardial involvement. Cardiac rhythm disturbances are not uncommon and may include new-onset atrial or ventricular arrhythmias or high-grade atrioventricular (AV) block. Of the 3055 adult patients with suspected acute or chronic

Abbreviations and Acronyms

AV = atrioventricular
CAR = coxsackie-adenovirus receptor
CVB3 = coxsackievirus B3
DCM = dilated cardiomyopathy
EAM = experimental autoimmune myocarditis
ECG = electrocardiogram
EMB = endomyocardial biopsy
GCM = giant cell myocarditis
HAART = highly active antiretroviral therapy
HIV = human immunodeficiency virus
IL = interleukin
IVIG = intravenous immunoglobulin
MRI = magnetic resonance imaging
TNF = tumor necrosis factor
Tnt = troponin T
myocarditis who were screened in the European Study of the Epidemiology and Treatment of inflammatory Heart Disease, 41 72% had dyspnea, 32% had chest pain, and 18% had arrhythmias. Patients with fulminant myocarditis typically present with severe heart failure symptoms that may rapidly lead to cardiogenic shock, whereas patients with GCM commonly present with heart failure symptoms that relentlessly progress to probable early death despite optimal treatment.

**Children**

The clinical presentation in children varies according to age. Infants may have nonspecific symptoms including anxiousness, malaise, fever, poor appetite, tachypnea, tachycardia, and cyanosis. Symptoms in children greater than 2 years of age may also include chest pain, abdominal pain, myalgias, fatigue, cough, and edema. The severity of symptoms is dependent on the age of the child, as newborns or infants are often more severely affected. In a study of 31 children found to have definite myocarditis (n = 16) or probable myocarditis (n = 15), the most common findings during initial presentation to the emergency department were respiratory distress (68%); tachycardia (58%); lethargy (39%); hepatomegaly (36%); emergency department were respiratory distress (68%); tachycardia, and cyanosis. Symptoms in children greater than 2 years of age may also include chest pain, abdominal pain, myalgias, fatigue, cough, and edema. The severity of symptoms is dependent on the age of the child, as newborns or infants are often more severely affected. In a study of 31 children found to have definite myocarditis (n = 16) or probable myocarditis (n = 15), the most common findings during initial presentation to the emergency department were respiratory distress (68%); tachycardia (58%); lethargy (39%); hepatomegaly (36%); abnormal heart sounds, including murmur (32%); and fever (30%). 42 Children, particularly infants, often have a more fulminant presentation than adults and may require advanced circulatory and respiratory support in early stages of their disease. 43

**Diagnosis**

**Electrocardiogram**

Although widely used as a screening tool, the sensitivity of electrocardiogram (ECG) for myocarditis is only 47%. 44 The most common ECG findings are nonspecific T-wave changes. Occasionally, the ECG changes may mimic acute myocardial infarction or pericarditis with ST-segment elevation, ST-segment depression, PR depression, and pathologic Q waves. 45, 46 In referral populations, new-onset supraventricular or ventricular arrhythmias occur in up to 55% of patients. 47 These tachyarrhythmias are often nonsustained and rarely cause hemodynamic compromise. The presence of abnormal QRS complexes, northwest axis deviation, or new left bundle branch block is associated with higher rates of death or cardiac transplantation. 19, 44, 48, 49

**Chest x-ray**

Chest x-ray may show cardiomegaly due to chamber dilatation, pericardial effusion, or both. Additional findings may include pulmonary venous congestion, interstitial infiltrates, and pleural effusions.

**Laboratory**

Non-specific serum markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein, and leukocyte count, are often elevated but are not used to make the diagnosis of acute myocarditis. Elevated levels of serum Fas and Fas ligand on initial presentation are associated with increased mortality in patients with acute myocarditis, 50 whereas elevated serum levels of interleukin-10 predict a poor prognosis in patients with fulminant myocarditis. 51

Cardiac biomarkers of myocardial injury are not elevated in most patients with myocarditis 52 but, if elevated, may be helpful to confirm the diagnosis. Increased serum concentrations of troponin I (TnI) or troponin T (TnT) are more common than increased levels of creatinine kinase or creatinine kinase-MB in both adults and children with acute myocarditis. 52- 55 Higher levels of TnT have been shown to be a prognostic marker for poor outcome in adult patients presenting with acute myocarditis. 51 Troponin I has high specificity (89%) and low sensitivity (34%) in adults presenting with acute myocarditis, 52 whereas in children, TnT has been reported to have a specificity of 83% and a sensitivity of 71%. 55

**Echocardiography**

Echocardiography is useful for evaluating cardiac chamber size, wall thickness, systolic and diastolic functions, and the presence of intracavitary thrombi. Its most prominent role is to rule out other causes of heart failure. There are no specific echocardiographic features of myocarditis, as patterns consistent with dilated, hypertrophic, and ischemic cardiomyopathies have all been described in patients with histologically proven myocarditis. 56

| Table 1 |
| Proposed cardiac MRI diagnostic criteria for myocarditis |
| A. In the setting of clinically suspected myocarditis, cardiac MRI findings are consistent with myocardial inflammation if at least 2 of the following criteria are present: |
| 1. Regional or global myocardial signal intensity increase in T2-weighted images |
| 2. Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images |
| 3. There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (delayed enhancement) |
| B. Cardiac MRI study is consistent with myocardite injury and/or scar caused by myocardial inflammation if criterion 3 is present |
| C. A repeat cardiac MRI study between 1 to 2 weeks after the initial cardiac MRI study is recommended if |
| • None of the criteria are present, but onset of symptoms is very recent, and there is strong clinical evidence for myocardial inflammation |
| • One of the criteria is present |
| D. The presence of left ventricular dysfunction or pericardial effusion provides additional supportive evidence for myocarditis |
ventricular systolic dysfunction is common, whereas right ventricular dysfunction is relatively uncommon. The presence of right ventricular dysfunction is important, however, as it was the most powerful predictor of death or need for cardiac transplantation in a series of 23 patients with biopsy-confirmed myocarditis. Segmental or global wall motion abnormalities are often present and may mimic myocardial infarction.

Diastolic filling patterns are abnormal in most patients, with a restrictive pattern frequently present. Ventricular thrombi have been noted in up to 25% of patients. Pericardial effusion, typically small, is not uncommon. Patients with fulminant myocarditis tend to present with small cardiac chambers and thickened walls, whereas those with acute myocarditis have marked left ventricular dilation and normal wall thickness.

### Cardiac MRI

Cardiac MRI is being used with increasing frequency for noninvasive assessment of patients with suspected myocarditis. With a unique potential for tissue characterization, particularly with the use of T1- and T2-weighted images, cardiac MRI can evaluate 3 markers of tissue injury, that is, intracellular and interstitial edema, hyperemia and capillary leakage, and necrosis and fibrosis.

A recent white paper written by the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis states that a cardiac MRI study should be performed in symptomatic patients with clinical suspicion of myocarditis in whom the MRI results will affect clinical management. Three imaging criteria for confirming the diagnosis of myocarditis (the “Lake Louise Criteria”) by cardiac MRI have been proposed (Table 1). When 2 or more of the 3 criteria are positive, myocardial inflammation can be predicted with a diagnostic accuracy of 78%; if only delayed, postgadolinium enhancement imaging is performed, the diagnostic accuracy drops to 68%.

Contrast cardiac MRI may be used to direct EMB. In a study by Mahrholdt et al, histopathologic evaluation of biopsy specimens directed by contrast cardiac MRI with delayed enhancement revealed active myocarditis in 19 of 21 patients. In contrast, when biopsy could not be obtained from the region of contrast enhancement, active myocarditis was found in only 1 of 11 patients.

### Endomyocardial biopsy

The role of EMB in the evaluation of suspected myocarditis was recently addressed in a scientific statement by the American College of Cardiology and the European Society of Cardiology. Fourteen scenarios are described, only 2 of which received a class I recommendation for EMB. The first of these 2 scenarios describes the classic presentation of fulminant myocarditis, that is, unexplained new-onset heart failure symptoms less than 2 weeks in duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise. The second scenario describes the distinctive clinical picture associated with GCM, that is, unexplained new-onset heart failure symptoms 2 weeks to 3 months in duration associated with a dilated left ventricle and new ventricular arrhythmias, high-degree AV heart block, or failure to respond to usual care within 1 to 2 weeks.

The role of EMB in patients who do not present with these clinical scenarios is not well established. Patients with 1 of the 2 indications described above should undergo EMB at a medical center with special expertise in this procedure. Although the complication rate is low, death may occur in even the most experienced hands.

### Etiology

#### Infectious

A variety of infectious and noninfectious diseases can cause myocarditis (Table 2). Viral infection is the most common cause in Western Europe and North America, with adenovirus and enterovirus (including coxsackievirus) historically being the most frequently identified viruses. Recently, the most commonly detected viral genomes in EMB samples were parvovirus B-19 and human herpesvirus-6. Serologic studies, predominantly in Japan, have linked the hepatitis C virus to myocarditis and DCM. Other viruses associated with myocarditis less frequently include cytomegalovirus, herpes simplex virus, and Epstein-Barr virus. Coinfection with 2 more viruses has been found in more than 25% of myocarditis patients.

Human immunodeficiency virus (HIV) has been associated with myocarditis and DCM. Although direct myocardial damage by the HIV virus is infrequent, cardiomyopathy in HIV-infected patients may be caused by coinfections, antiretroviral medications, or inhibition of cardiac contractility by HIV type 1 glycoprotein 120. In studies performed before the highly active antiretroviral therapy (HAART) era, myocarditis was identified in more than 50% of patients. Since the introduction of HAART, the incidence of myocarditis in HIV-infected patients living in developed countries has significantly decreased. In developing countries, however, where the availability of HAART is limited, the incidence of HIV-associated myocarditis continues to increase.

Although numerous bacterial infections can cause myocarditis, bacterial-induced myocarditis is far less common than viral-induced myocarditis. Toxin-producing bacteria, including clostridium and diphtheria, can cause severe myocardial damage. Bacteremia from any source may result in myocarditis, with the most common pathogens being meningococcus, streptococcus, and Listeria.

The spirochete Borrelia burgdorferi causes Lyme disease, which can result in both acute and chronic...
Table 2

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Bacterial: Burkholderia pseudomallei (melioidosis), Brucella, Chlamydia (especially Chlamydia pneumonia and Chlamydia psittaciosis), Corynebacterium diphtheriae (diphtheria), Francisella tularensis (tularemia), Haemophilus influenzae, gonococcus, Clostridium, Legionella pneumophila (Legionnaire disease), Mycobacterium tuberculosis, Neisseria meningitidis, Salmonella, Staphylococcus, Streptococcus A (rheumatic fever), Streptococcus pneumoniae, syphilis, tetanus, tularemia, Vibrio cholera</td>
</tr>
<tr>
<td></td>
<td>Viral: adenovirus, arbovirus, Chikungunya virus, Cytomegalovirus, echorvirus, Enterovirus (Coxsackie B), Epstein-Barr virus, Flavivirus (dengue fever and yellow fever), hepatitis B virus, hepatitis C virus, herpes viruses (human herpesvirus-6), HIV/AIDS, influenza A and B viruses, Parvovirus (parvovirus B-19), mumps virus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, rubella virus, varicella virus, variola virus (smallpox)</td>
</tr>
<tr>
<td></td>
<td>Protozoal: Balantidium, Entamoeba histolytica (amebiasis), Leishmania, Plasmodium falciparum (malaria), Sarcocystis, Trypanosoma cruzi (Chagas disease), Trypanosoma brucei (African sleeping sickness), Toxoplasma gondii (toxoplasmosis)</td>
</tr>
<tr>
<td></td>
<td>Helminthic: Ascaris, Echinococcus granulosus, Heterophyes, Paragonimus westermani, Schistosoma, Strongyloides stercoralis, Taenia solium (cysticercosis), Toxocara canis (visceral larva migrans), Trichinella spiralis, Wuchereria bancrofti (filariasis)</td>
</tr>
<tr>
<td></td>
<td>Environmental: arsenic, carbon monoxide, copper, iron, lead</td>
</tr>
<tr>
<td></td>
<td>Environmental: arsenic, carbon monoxide, copper, iron, lead</td>
</tr>
</tbody>
</table>

Most common etiologies are rendered in **bold**.

myocarditis. A recent study of 207 children with early disseminated Lyme disease found that 33 (16%) had mild to fulminant myocarditis, 14 (42%) of whom had advanced AV heart block. Although full recovery is the norm, Lyme carditis sometimes persists and may lead to chronic heart failure.

Infection with the protozoa Trypanosoma cruzi (Chagas disease), common in Central and South America and occasionally seen in the United States, can present as acute myocarditis or chronic cardiomyopathy. The mechanism is thought to be immune activation after infection. Pericardial effusion is common in the acute phase, whereas the chronic phase is often characterized by DCM, segmental wall motion abnormalities, and left ventricular apical aneurysm. Electrocardiographic changes include right bundle branch block, left anterior fascicular block, and AV block.

**Toxins and hypersensitivity reactions**

Drugs can cause myocardial inflammation by either a direct toxic effect on the heart or by inducing hypersensitivity reactions. Anthracycline toxicity is relatively common, and cocaine has been increasingly implicated...
in acute myocarditis, but numerous other medications can cause cardiotoxicity including cyclophosphamide, phenytoin, zidovudine, and amphetamines. Drug-induced hypersensitivity reactions can cause an eosinophilic myocarditis that often responds to withdrawal of the offending medication, though adjuvant corticosteroid therapy is often necessary. Medications implicated in hypersensitivity myocarditis include several anticonvulsants and antipsychotics as well as a number of antibiotics. The possibility of drug-induced hypersensitivity myocarditis should be considered in any patient taking either prescription or over the counter medications, particularly if eosinophilia or eosinophilic myocardial infiltration is present.

Autoimmune and systemic diseases

Systemic diseases, particularly Churg-Strauss syndrome, cancer, and hypereosinophilic syndrome, as well as certain protozoal, helminthic, and parasitic infections, may also induce eosinophilic myocarditis. Eosinophilic myocarditis has been reported after vaccination for several diseases including tetanus and smallpox. Clinical manifestations of eosinophilic myocarditis may include congestive heart failure, constitutional symptoms, rash, cough, endocardial and valvular fibrosis, and endocardial thrombi. Necrotizing eosinophilic myocarditis is a rare aggressive form of eosinophilic myocarditis with a short-term onset and high death rate.

Idiopathic GCM is a rare, virulent, autoimmune form of myocarditis histologically defined by the presence of multinucleated giant cells, a lymphocytic inflammatory infiltrate, and myocyte necrosis (Fig 1A and B). This disease usually occurs in young adults and carries a high risk of death unless cardiac transplantation is performed. It is considered to be autoimmune because of its association with other autoimmune disorders, thymoma, and drug hypersensitivity. Rare in adults, GCM is rarer still in children and is associated with immune-mediated disease in other organs. Cardiac sarcoidosis is another unusual form of idiopathic myocarditis that is distinct from GCM in that it is characterized histologically by interstitial granulomas without myocyte necrosis and has a lower fatality rate. Patients tend to present with either chronic DCM with new ventricular arrhythmias or high-grade AV block or do not respond to optimal therapy.

Pathogenic mechanisms

Host factors

Factors that determine susceptibility to viral myocarditis are not fully known, although a variety of factors such as malnutrition, pregnancy, sex hormones, and age have been implicated. Genetic host factors, including major histocompatibility haplotype, HLA-DQ locus, and CD45 polymorphisms, may be important determinants of early viral infection. Other host factors including selenium deficiency, vitamin E deficiency, and mercury exposure have been reported to increase viral virulence. Viral factors, including genome phenotype, have been shown to affect cardiovirulence as well.

Viral entry into cardiomyocytes

Most of our understanding of the pathophysiology of viral and autoimmune myocarditis comes from studies in rodent models in which susceptible strains of mice are infected with a cardiotropic virus such as coxsackievirus B. The virus is taken up in the cell by endothelial receptors, most notably the coxsackie-adenovirus receptor (CAR). In addition to CAR, coxsackievirus serotypes B1, B3, and B5 use decay-accelerating factor and adenoviruses use αv integrins as coreceptors for viral entry. Differential binding to decay-accelerating factor increases viral virulence in coxsackievirus B infections.

Coxsackie-adenovirus receptor is highly expressed in the brain and heart, peaking in the perinatal period with subsequent overall levels decreasing with age. In immature hearts, CAR is detected on the entire surface of
cardiac myocytes, whereas in the adult heart, CAR is predominantly found in the intercalated disks. The expression level and the location of CAR in neonates and infants may help to explain the susceptibility of this population to coxsackievirus B3 (CVB3)-mediated myocarditis. A recent study involving inducible CAR knockout mice provided the first genetic evidence that CAR is the receptor for coxsackievirus in vivo while also demonstrating that the elimination of CAR blocked virus entry into myocytes and prevented signs of inflammatory cardiomyopathy. Previously, it was thought that myocarditis was primarily an autoimmune-mediated disease due to the presence of autoantibodies directed against cardiac myocyte proteins in patients with myocarditis, but the lack of myocardial damage noted in the CAR knockout mice suggests that the primary mechanism in viral myocarditis may be viral mediated, at least in the acute phase.

Innate immune response

The duration and degree of the innate immune response to viral infection has a crucial role in the development of myocarditis (Fig 2). A variety of inflammatory mediators, including cytokines such as tumor necrosis factor (TNF), nitric oxide, toll-like receptors, and complement are up-regulated. Studies in mice have shown that these mediators may play a dual role in the development of viral-induced myocarditis. For instance, one murine model demonstrated increased TNF levels not only decreased viral load but also led to an exaggerated immune response and late mortality. Nitric oxide not only inhibits viral replication but also contributes to the development of cardiomyopathy by enhancing ongoing myocardial injury. Toll-like receptors and myeloid differentiation factor-88 (MyD88), an adapter molecule for toll-like receptors, minimize viral replication in the heart, but MyD88 appears to significantly affect the severity of myocardial inflammation. Complement amplifies not only the innate immune response but also the adaptive immune response, increasing susceptibility to autoimmune myocarditis and progression to chronic DCM.

Direct viral injury

Viruses that evade the innate immune system replicate, producing viral proteins that cause direct myocardial injury. Coxsackievirus B3 infection in mice with severe combined immune deficiency induces myocardial injury. Picornavirus protease 2A has been shown to inhibit host cell protein synthesis, and CVB3 protease 2A cleaves the host protein dystrophin, which may induce cardiomyopathy. In addition to their proteolytic activity in myocytes, CVB3 proteases 2A and 3C can induce apoptosis, causing further cardiomyocyte injury. Inhibition of these viral proteases could be a novel target in the treatment of viral-induced myocarditis.

Acquired immune response

Cell-mediated immunity plays a critical role in the development of both viral and autoimmune myocarditis (Fig 2). The inflammatory infiltrate observed in myocardial lesions of myocarditis consists of more than 70% mononuclear cells, primarily monocytes, macrophages, and T lymphocytes. Inhibition of monocyte chemoattractant protein 1 and macrophage inflammatory protein 1α reduces the severity and prevalence of myocarditis in
experimental autoimmune myocarditis (EAM) mice. Helper T cell types 1 and 2 (Th1 and Th2) secrete cytokines such as TNF and interleukins, which are associated with the development of autoimmune cardiomyopathy, within 6 to 12 hours of viral infection in susceptible mice. Helper T cell type 17 (TH17) produces interleukin-17, which drives the development of severe autoimmune myocarditis in interferon-γ–deficient EAM mice. Inhibition of T lymphocyte proliferation and activation in EAM mice attenuates the immune response and decreases the severity of myocarditis.

Acute cardiac injury activates the adaptive immune response that further mediates cardiac damage. CD4+ T lymphocytes play a critical in the induction of autoimmune myocarditis, not only due to their production of key cytokines but also due their production of antibodies and autoantibodies. Animals developing autoimmune myocarditis after CVB3 infection develop antibodies to multiple cardiac antigens, including epitopes in the S2 hinge region of cardiac myosin. Autoantibodies to numerous cardiac antigens are common in patients with myocarditis and DCM and may actually precede the development of disease. In particular, antibodies against cardiac β1 adrenergic receptors have been found in the sera of patients with myocarditis and DCM, and removal of the circulating β1 adrenergic receptor autoantibody in patients with DCM by immunoadsorption improved cardiac function. Antibodies against TnI lead to severe inflammation and fibrosis in the myocardium in experimental mice, leading to cardiac dilatation and reduced survival, although antibodies against TnT have not produced a similar immunologic response.

In most patients with viral myocarditis, the pathogen is cleared and the immune system is down-regulated with no further adverse effects. However, in a minority of patients, the virus is not cleared, resulting in persistent myocyte damage and myocardial inflammation due to the immune response to cardiac autoantibodies (Fig 2).

**Treatment**

**Heart failure therapy**

Most patients with acute myocarditis presenting with DCM respond well to standard heart failure therapy including diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, and the introduction of β-blockers such as bisoprolol, metoprolol succinate, or carvedilol once they are clinically stable. Digoxin should be used with caution and only in low doses in patients with viral myocarditis because administration of digoxin in high doses to mice with viral-induced myocarditis increased mortality. Amlodipine improved survival, ratio of heart weight to body weight, and the histopathologic grades of myocardial lesions in one study in a murine model of viral myocarditis, whereas nifedipine decreased the activation of proinflammatory cytokines in another study in mice with viral myocarditis; however, no data on use of calcium channel blockers in humans with viral myocarditis has been published. Patients with high filling pressures may require support with intravenous vasodilators, whereas patients who present with severe symptoms may require intravenous inotropic medications. Offending agents, including cardiotoxic drugs and alcohol, should be discontinued.

**Nonsteroidal antiinflammatory drugs**

Treatment with nonsteroidal antiinflammatory drugs has not proven to be effective in several murine models and should actually be avoided, as use of these medications in murine models of acute viral myocarditis resulted in increased inflammation and higher mortality.

**Mechanical circulatory support and transplantation**

Mechanical circulatory support may be effective in patients presenting with cardiogenic shock. Extracorporeal membrane oxygenation support may be especially beneficial for adult and pediatric patients with fulminant myocarditis with profound shock, as short-term recovery is expected. For patients with cardiogenic shock due to acute myocarditis who deteriorate despite optimal medical management, recovery is more likely to be prolonged and implantation of a ventricular assist device as a bridge to transplantation or recovery may be effective. Cardiac transplantation is reserved for those patients who are refractory to optimal medical therapy and mechanical circulatory support.

**Antiviral treatment**

As viral infection is the most common cause of myocarditis, it would seem plausible that treatment with antiviral medications or antiviral vaccines would be beneficial. It is clear that viral genomes are present in a subset of patients with acute myocarditis, but it remains uncertain whether this affects mortality or the need for cardiac transplantation. Data regarding antiviral treatment in myocarditis are limited to murine models and a few case series in humans, but results have been promising. Antiviral therapy with ribavirin or interferon in murine viral myocarditis prevented onset of cardiomyopathy, reduced the severity of the disease, and decreased mortality. In the single case series of antiviral therapy use in humans with fulminant myocarditis, ribavirin therapy did not prove effective. This is not surprising, as most patients with acute myocarditis are diagnosed several weeks after viral infection, so it is unlikely that antiviral therapy administered once myocarditis has been confirmed would provide much benefit.
In patients with chronic DCM and persistent viral genomes, however, treatment with interferon resulted in the elimination of the viral genomes and improved left ventricular function.\textsuperscript{160}

**Immunosuppressive treatment**

Numerous studies have investigated the use of immunosuppressants for treatment of acute myocarditis and DCM (Table 3). Early results of randomized controlled trials enrolling adult patients with acute myocarditis and idiopathic DCM were disappointing, as treatment with immunosuppressants such as prednisone, cyclosporin, and azathioprine showed little or no treatment effect.\textsuperscript{17,168} In patients with GCM, however, long-term survival is improved with treatment with cyclosporin and corticosteroids, and in fact, withdrawal of immunosuppression in this population has at times resulted in increased risk of recurrent, occasionally fatal, GCM.\textsuperscript{23,165} Several case series and a small trial in children have demonstrated that immunosuppressive treatment improved left ventricular function and arrhythmias,\textsuperscript{166,173,174} but there have been no

**Table 3**

<table>
<thead>
<tr>
<th>Treatment Trial</th>
<th>Trial Type</th>
<th>Disease</th>
<th>No. of Patients</th>
<th>Agent(s)</th>
<th>Primary Outcome Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults: Acute Myocarditis</td>
<td>Prospective</td>
<td>Acute lymphocytic myocarditis</td>
<td>9</td>
<td>Prednisone plus azathioprine</td>
<td>Improvement in LVEF</td>
<td>No treatment benefit</td>
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<tr>
<td>Jones,\textsuperscript{161} 1991</td>
<td>RCT</td>
<td>Acute lymphocytic myocarditis</td>
<td>17</td>
<td>Prednisone plus either cyclosporine or azathioprine</td>
<td>Improvement in LVEF at 3 mo</td>
<td>Significant treatment benefit</td>
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<td>Maisch,\textsuperscript{162} 1995</td>
<td>RCT</td>
<td>Acute lymphocytic myocarditis</td>
<td>111</td>
<td>Prednisone plus cyclosporine</td>
<td>Improvement in LVEF at 6 mo</td>
<td>No treatment benefit</td>
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<tr>
<td>Mason,\textsuperscript{17} 1995: The Myocarditis Treatment Trial</td>
<td>Prospective</td>
<td>Acute lymphocytic myocarditis</td>
<td>10</td>
<td>IVIG</td>
<td>Improvement in LVEF at 1 y</td>
<td>Treatment benefit</td>
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<td>McNamara,\textsuperscript{163} 1997</td>
<td>RCT</td>
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<td>IVIG</td>
<td>Improvement in LVEF at 6 mo</td>
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<tr>
<td>McNamara,\textsuperscript{164} 1999: Immune Modulation for Acute Cardiomyopathy</td>
<td>Prospective</td>
<td>GCM</td>
<td>11</td>
<td>Prednisone plus cyclosporine</td>
<td>Survival at 1 y</td>
<td>Treatment benefit</td>
</tr>
<tr>
<td>Cooper,\textsuperscript{165} 2008: Giant Cell Myocarditis Treatment Trial</td>
<td>Retrospective</td>
<td>Acute myocarditis</td>
<td>13</td>
<td>Prednisone (1 patient also received azathioprine)</td>
<td>Clinical improvement (ECG changes, heart size, ejection fraction)</td>
<td>Small treatment benefit</td>
</tr>
<tr>
<td>Chan,\textsuperscript{166} 1991</td>
<td>RCT</td>
<td>Acute myocarditis</td>
<td>21</td>
<td>IVIG</td>
<td>Survival and improvement in LVEF at 1 y</td>
<td>Treatment benefit</td>
</tr>
<tr>
<td>Chronic Myocarditis/DCM</td>
<td>RCT</td>
<td>Idiopathic DCM</td>
<td>102</td>
<td>Prednisone</td>
<td>Improvement in LVEF at 3 mo</td>
<td>Small treatment benefit</td>
</tr>
<tr>
<td>Parrillo,\textsuperscript{168} 1989</td>
<td>RCT</td>
<td>DCM</td>
<td>84</td>
<td>Prednisone plus azathioprine</td>
<td>Composite of death, heart transplantation, and hospital readmission at 2 y</td>
<td>No treatment benefit (secondary outcome benefit)</td>
</tr>
<tr>
<td>Wojnicz,\textsuperscript{169} 2001</td>
<td>RCT</td>
<td>Active lymphocytic myocarditis with chronic heart failure</td>
<td>41</td>
<td>Prednisone and azathioprine</td>
<td>Improvement in LVEF at 1 y</td>
<td>Treatment benefit for patients with no viral genome in the myocardium</td>
</tr>
<tr>
<td>Frustaci,\textsuperscript{170} 2003</td>
<td>RCT</td>
<td>DCM</td>
<td>40</td>
<td>IVIG</td>
<td>Improvement in LVEF at 26 wk</td>
<td>Treatment benefit</td>
</tr>
<tr>
<td>Gullestad,\textsuperscript{171} 2001</td>
<td>RCT</td>
<td>Chronic virus-positive DCM</td>
<td>22</td>
<td>Interferon-(\beta)</td>
<td>Viral clearance and improvement in LV size and LVEF at 6 mo</td>
<td>Treatment benefit for both outcomes</td>
</tr>
<tr>
<td>Kuhl,\textsuperscript{160} 2003</td>
<td>RCT</td>
<td>Chronic virus-negative DCM</td>
<td>85</td>
<td>Prednisone and azathioprine</td>
<td>Improvement in LVEF at 6 mo</td>
<td>Significant treatment benefit</td>
</tr>
</tbody>
</table>

**Abbreviations:** LVEF indicates left ventricular ejection fraction; RCT, randomized controlled trial.
large randomized controlled trials in children to validate these outcomes. In any case, caution must be used in interpreting these data, as the improvement seen may at least partially be due to the natural history of the disease in which spontaneous recovery frequently occurs.

In contrast, immunosuppression may be beneficial in treating patients with chronic DCM unresponsive to standard heart failure therapy. Several studies evaluating immunosuppressive treatment of chronic virus-negative DCM, including the recently completed Therapy in Inflammatory Dilated Cardiomyopathy trial, have shown that the use of azathioprine and prednisone results in significant improvement in left ventricular ejection fraction and New York Heart Association class.\textsuperscript{169,170,172} These data suggest that immunosuppression may prove beneficial in patients with chronic virus-negative DCM that persists despite optimal medical treatment.

**Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) has both antiviral and immunomodulating effects, suggesting that it might be an effective therapy in acute viral myocarditis. The recent Immune Modulation for Acute Cardiomyopathy trial, however, demonstrated that adult patients with recent onset of myocarditis or DCM who were treated with IVIG fared no better than similar patients treated with placebo.\textsuperscript{175} There are no randomized controlled trials investigating the use of IVIG to treat children with acute myocarditis, but several case series have shown that use of high-dose IVIG to treat acute myocarditis in this population leads to improved recovery of left ventricular function and better survival.\textsuperscript{53,167} Routine use of IVIG is therefore not recommended in adults but may be considered in select pediatric cases with acute myocarditis.

**Antiarrhythmic treatment**

High-grade AV block and tachyarrhythmias may be treated with appropriate medications and placement of a temporary or permanent pacemaker, as needed. Arrhythmias usually resolve after several weeks. Patients with symptomatic or sustained ventricular tachycardia may require antiarrhythmic therapy or possibly an implantable cardioverter-defibrillator or cardiac transplantation if arrhythmias persist after the acute inflammatory phase.

**Physical activity**

Animal studies have shown that sustained aerobic exercise during acute viral myocarditis leads to increased mortality.\textsuperscript{176} Based on these results and the knowledge that myocarditis is a cause of sudden death in young athletes,\textsuperscript{177} patients with acute myocarditis are advised to withdraw from competitive sports and other vigorous exercise for up to 6 months or longer after onset of symptoms, with length of recuperation required based on recovery of left ventricular function.\textsuperscript{178}

**Prognosis**

Prognosis is excellent for adult patients with acute lymphocytic myocarditis with mild symptoms and preserved left ventricular ejection fraction, as most of them spontaneously improve without residual sequelae. In contrast, the Myocarditis Treatment Trial demonstrated that symptomatic adult patients who present with heart failure symptoms and a left ventricular ejection fraction less than 45% at baseline have a 4-year mortality of 56%.\textsuperscript{17} These results were obtained before the routine use of β-blockers, however, so prognosis in the current era has likely improved. Predictors of increased likelihood of death or need for cardiac transplantation include syncope,\textsuperscript{179} right ventricular systolic dysfunction,\textsuperscript{58} elevated pulmonary artery pressure,\textsuperscript{180} and advanced New York Heart Association functional class.\textsuperscript{5} Elevated levels of Fas, Fas ligand, TNF, and IL-10\textsuperscript{50,51,181,182} as well as immunohistologic signs of inflammation (CD3 and/or CD68),\textsuperscript{5} are also predictors of increased risk of death.

Less information is available on the natural history of myocarditis in children. One study of 70 children with acute myocarditis reported that 73% of patients had histologic resolution of myocarditis at 6 months and 96% of patients survived to 1 year. Another study of 41 children with acute myocarditis who were treated with immunosuppression reported that at 5 years, most patients had complete recovery, whereas a quarter of patients died or required cardiac transplantation.\textsuperscript{183} Children who do not fully recover may develop chronic DCM that may result in death or cardiac transplantation up to 12 years after diagnosis.\textsuperscript{35}

Patients with fulminant myocarditis who survive the acute phase have an excellent long-term prognosis and are more likely to experience complete recovery of left ventricular function compared with patients with acute myocarditis.\textsuperscript{180} Children and adults with GCM, on the other hand, have a median survival of less than 6 months and usually require cardiac transplantation. Transplant-free survival is better in patients with cardiac sarcoidosis than for patients with GCM, with a 70% 5-year survival rate.\textsuperscript{98} Most patients with Lyme carditis experience complete recovery.

Survival among patients undergoing heart transplant for treatment of acute myocarditis is similar to that of patients undergoing transplant for other cardiac diseases.\textsuperscript{184} Patients with GCM may be successfully treated with heart transplantation even though GCM recurs in up to 25% of transplanted adult hearts.\textsuperscript{23} Transplanted hearts with recurrent GCM may be effectively treated with augmented immunosuppression in most cases. Recurrent GCM with or without immunosuppressive treatment may be more virulent in children than in adults.\textsuperscript{185}
Prevention

Specific strategies for the prevention of myocarditis have yet to be determined. To the extent that they have eliminated the diseases, vaccination against measles, mumps, rubella, poliomyelitis, and influenza has made myocarditis secondary to these diseases quite rare and raises the question of whether vaccinations against other cardiotropic viruses may prevent myocarditis in the future. Murine models have demonstrated that vaccination is protective against viral infection and prevents myocardial damage, but there have been no vaccination trials in humans. Given the low incidence of myocarditis and the cost of developing these vaccines, it is doubtful that antiviral vaccines to combat this disease will be developed in the near future.

Summary and future directions

Myocarditis is a potentially life-threatening disease that primarily affects children and young adults with sometimes devastating consequences, including sudden death. The primary long-term consequences are DCM and chronic heart failure. Although much progress has been made in recent years in the diagnosis, pathophysiology, and treatment of this disease, numerous questions remain and indicate the need for further investigation. Noninvasive strategies for confirming the diagnosis of myocarditis, including cardiac MRI, are promising but require additional validation. The identification of novel biomarkers of cardiac inflammation in peripheral blood, including analysis of messenger RNA and specific proteins, is underway. If a panel of blood-based biomarkers with high sensitivity and specificity can be developed as a noninvasive diagnostic tool, it may decrease the need for EMB. Although the pathophysiology of myocarditis has been studied in great detail in experimental animal models, research on the cellular processes contributing to myocardial damage in human myocarditis patients remains limited. Ongoing research efforts in this area that may lead to novel treatment strategies directed toward pathway-specific targets include the identification of genomic profiles that affect individual susceptibility to myocarditis or predict the likelihood of recovery.

Statement of Conflict of Interest

The authors declare that there are no conflicts of interest.

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