

# Acute myocarditis

Anjan S. Batra, MD, and Alan B. Lewis, MD

Myocarditis is defined as inflammation of the myocardium accompanied by myocellular necrosis. Acute myocarditis must be considered in patients who present with recent onset of cardiac failure or arrhythmia. Often there is a history of an antecedent flu-like illness. Fulminant myocarditis is a distinct entity characterized by sudden onset of severe congestive heart failure or cardiogenic shock, usually following a flu-like illness. Giant cell myocarditis is a rare, frequently fatal disorder of unknown origin characterized by presence of giant cell inflammatory infiltrate in the myocardium. In recent years we have made good progress in understanding the causes, pathogenesis, natural history, diagnosis, and treatment of myocarditis. However, our knowledge is still far from complete. New information that extends our understanding of myocarditis is being reported constantly. This review summarizes recent advances in myocarditis, with an emphasis on the literature during the last year. *Curr Opin Pediatr* 2001, 13:234–239 © 2001

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Division of Cardiology, Childrens Hospital Los Angeles and the University of Southern California Los Angeles, California, USA.

Correspondence to Alan B. Lewis, MD, Division of Cardiology, Childrens Hospital Los Angeles, MS #34 4650 Sunset Blvd, Los Angeles, CA 90027, USA, e-mail: alewis@chla.usc.edu

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## Abbreviations

<b>CAR</b>	coxsackie-adenovirus receptor
<b>BVAD</b>	biventricular assist device
<b>ECMO</b>	extracorporeal membrane oxygenation
<b>LVAD</b>	left ventricular assist device
<b>MRI</b>	magnetic resonance imaging
<b>PCR</b>	polymerase chain reaction

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Myocarditis is defined as inflammation of the myocardium accompanied by myocellular necrosis. Acute myocarditis must be considered in patients who present with recent onset of cardiac failure or arrhythmia, though the onset of clinical cardiac symptoms may be vague in many patients. Often there is a history of an antecedent flu-like illness. In contrast, fulminant myocarditis is a distinct entity characterized by the sudden onset of severe congestive heart failure or cardiogenic shock, usually following a flu-like illness. Giant cell myocarditis is a rare, frequently fatal disorder of unknown origin characterized by presence of giant cell inflammatory infiltrate in the myocardium [1•]. Despite these apparent distinctions there may be overlap between these clinical entities. In recent years we have come a long way in understanding the etiology, pathogenesis, natural history, diagnosis, and treatment of myocarditis. However, our knowledge is still far from complete. New information that extends our understanding of myocarditis is reported constantly. This review summarizes recent advances in myocarditis, with an emphasis on the literature during the last year.

## Etiology and incidence

The etiology of myocarditis has been associated with various infections, systemic diseases, drugs, and toxins. Among the infectious agents, a wide array of organisms, including viral, bacterial, rickettsial, fungal, and parasitic organisms, have been implicated as causative agents [2••]. Organisms like *Trypanosoma cruzi* (Chagas disease) and *Corynebacterium diphtheriae* (diphtheria) are common causes of myocarditis worldwide but are found infrequently in the United States [3,4]. In the United States and Europe, viruses are probably the most important cause of myocarditis, with coxsackievirus the most common viral pathogen (Table 1). Adenovirus has been implicated recently as an important cause of myocarditis as well [5]. Other viruses that have been reported to cause myocarditis in recent literature include Epstein-Barr virus [6], human herpesvirus [7], parvovirus B19 [8], and hepatitis C virus [9]. Among the toxins, cocaine abuse has been associated with the acute onset of cardiac dysfunction [10]. Nevertheless, the exact cause remains unknown in the majority of patients with presumed myocarditis. Giant cell myocarditis is a rare and frequently fatal disease characterized by widespread necrosis and degeneration of myocardial fibers. It may be associated with various systemic autoimmune diseases.

**Table 1. Viral causes of myocarditis**

Common causes	Uncommon/rare causes
Coxsackievirus	Cytomegalovirus
Adenovirus	Echovirus
	Epstein-Barr virus
	Human herpesvirus
	Parvovirus B19
	Hepatitis C
	Influenza A
	Respiratory syncytial virus
	Mumps virus
	HIV
	Rubella
	Measles

The number of cases of acute myocarditis appears to have declined since the 1980's. In a recent single institution report, the percentage of patients with an endomyocardial biopsy diagnosis of acute myocarditis decreased from 20% in 1985 to less than 2% in 1996 ( $P < 0.001$  for annual trend) [11••]. However, the number of cases of fulminant myocarditis in the same report remained relatively constant, at about one case per year.

Myocarditis has been implicated in sudden infant death syndrome. In a pathologic analysis of 331 infants who died from sudden infant death syndrome, 16% were found to have inflammatory infiltrates in the myocardium [12]. The incidence of biopsy-proven myocarditis in peripartum cardiomyopathy may be as high as 62% [13••]. Finally, there is also increasing evidence that a significant proportion of patients with dilated cardiomyopathy may have evidence of ongoing myocarditis [14••].

### Pathogenesis

Although viral infection is the most common initiating trigger of acute myocarditis, the subsequent autoimmune response appears to be the major contributing factor to cellular injury [15••]. Because myocarditis in humans is relatively rare, our understanding of the pathophysiology of myocarditis comes largely from animal models. Coxsackievirus B3-induced murine myocarditis is characterized by a transient initial phase followed by a secondary phase in susceptible strains. The initial phase, lasting up to 4 days, most likely reflects the direct cytopathic effect of the virus, and consists of focal myocyte necrosis and polymorphonuclear and monocytic infiltration. Virus can be detected from the myocardium in this early phase. The secondary phase of murine myocarditis appears to be the effect of altered immune regulation. Major histocompatibility complex class I and II molecules are important in presenting foreign antigens such as viruses to the immune system. The major histocompatibility complex-presenting cells in turn stimulate the produc-

tion of CD4+ T helper cells and CD8+ cytotoxic T cells, with subsequent production of proinflammatory cytokines. That cytokines play an important role in myocyte damage leading to dilated cardiomyopathy is suggested by the high incidence of cytokines, especially tumor necrosis factor- $\alpha$ , interleukin-6, and interleukin-8, in patients with myocarditis and dilated cardiomyopathy [16]. Conversely, other cytokines, like interleukin-10 and -12 may play a protective role in viral myocarditis [17,18]. Nitric oxide is produced in the heart and plays an important role in the murine model of coxsackievirus B3-induced myocarditis. Inducible nitric oxide synthase activity appears on day 4, peaks on day 8, and can be detected for 1 month after virus inoculation in the murine model [19•]. The high levels of nitric oxide, which appear to be a part of the immune defense against the virus, may be toxic to host tissue and may promote ventricular dilatation. T cells produced *de novo* in the bone marrow play a major role in the pathogenesis of the autoimmune myocarditis [20•].

The concept of myocarditis as an autoimmune phenomenon is supported by studies linking persistence of viral RNA in the myocardium with induction of autoantibodies. Patients with myocarditis often show autoantibodies against adenine nucleotide translocator [21] and cardiac myosin, and are associated with worse left ventricular systolic and diastolic function [22•].

Recently, there has been new insight into the duration of viral presence in the myocardium. Rapid, albeit incomplete, clearance of viral RNA from the myocardium has been demonstrated after the acute phase of coxsackievirus B3 myocarditis in the mouse [23•]. Nevertheless, viral RNA persisted in the myocardium beyond the resolution of inflammation and was still detectable in some animals 90 days after infection. Whether the persistence of virus plays a significant role in the pathogenesis of human myocarditis needs further investigation. Enteroviral RNA has been detected in up to 35% of patients with dilated cardiomyopathy, supporting the hypothesis that the latter may be a sequela of acute myocarditis and that persistence of viral RNA may promote the development of dilated cardiomyopathy [14]. Badorff *et al.* [24•] suggested a molecular mechanism through which enteroviral infection contributes to the pathogenesis of dilated cardiomyopathy. They demonstrated that purified coxsackievirus protease 2A cleaves dystrophin in infected myocytes, thereby damaging the myocardial cytoskeleton and leading to myocardial dysfunction.

Recently a specific myocardial receptor for adenovirus and coxsackievirus B, the coxsackie-adenovirus receptor (CAR), has been identified [25], providing a unifying concept for the cardiac tropism of these agents. The

CAR protein has been mapped to chromosome 2q11.2 [26]. Most recently, the specific amino-terminal immunoglobulin domain of CAR necessary for adenovirus binding has also been identified [27]. Manipulation of these binding sites has been shown to alter adenoviral binding [28]. The presence or expression of these receptors may determine the susceptibility of the host to viral myocarditis and may provide opportunities for innovative therapies.

There is emerging evidence to support the speculation that dilated cardiomyopathy develops as a consequence of myocarditis in a subgroup of genetically predisposed individuals. Asymptomatic first-degree relatives of patients with dilated cardiomyopathy have echocardiographic evidence of left ventricular dysfunction [29] and increased autoantibodies [30].

### Diagnosis

Despite an array of invasive and noninvasive diagnostic modalities, clinical criteria remain the most common diagnostic method for acute myocarditis (Table 2). Patients with acute myocarditis may present with a variety of clinical scenarios, ranging from asymptomatic with only subtle findings on an electrocardiogram or echocardiogram, to fulminant heart failure and death. Myocarditis may also mimic acute myocardial infarction in patients with angiographically normal coronary arteries [31]. The endomyocardial biopsy, using the Dallas criteria for histopathologic classification, has remained the gold standard for the diagnosis of acute myocarditis despite limited sensitivity and specificity. Testing for the presence of viral genome in endomyocardial biopsy specimens by polymerase chain reaction (PCR) has helped in providing further diagnostic and prognostic information. The European Study of Epidemiology and Treatment of Inflammatory Heart Disease (ESETCID) included immunohistochemical markers along with molecular techniques such as PCR and *in situ* hybridization, in addition to the Dallas criteria, to define acute and chronic myocarditis [32••]. The ESETCID found ongoing inflammation in 17.2% and detected virus in

11.8% of endomyocardial biopsies in patients with clinically suspected myocarditis.

The risk of perforation from endomyocardial biopsy may be increased in young patients with myocarditis, particularly those requiring inotropic support [33]. In view of the limited sensitivity and specificity of endomyocardial biopsy, emphasis is being placed on newer, less invasive, modalities of diagnosing myocarditis. PCR analyses of blood, peripheral fluid, and tracheal aspirates have been used to search for viral RNA. Unfortunately, blood and peripheral fluid PCR were rarely positive for viral genome [34]. However, tracheal aspirate samples in intubated patients had a strong correlation with the endomyocardial biopsy results [35]. Hence, tracheal aspirate PCR may emerge as a useful diagnostic alternative to endomyocardial biopsy in patients on mechanically assisted ventilation. The validity of tracheal aspirate PCR in nonintubated patients, however, needs further investigation.

Other noninvasive diagnostic modalities undergoing active research include assays for autoimmune serum markers and the induction of the major histocompatibility and intercellular adhesion molecules on cardiac myocytes. Serum protein levels of soluble Fas (sFas) and soluble Fas ligand (sFasL) appear to be promising serologic markers to predict the prognosis of acute myocarditis [36]. Creatine kinase MB fraction, troponin levels, and C-reactive protein are other serologic markers that may help in the diagnosis or prognosis of patients with myocarditis [37–39]. Increased levels of antibodies against adenine nucleotide translocator and myosin have been described in patients with myocarditis, and these levels have been found to correlate with worse left ventricular function over time [21,22•].

Additional noninvasive strategies being used to identify myocarditis include autoimmune scintigraphy, contrast enhanced magnetic resonance imaging (MRI), cine magnetic resonance angiography and echocardiographic digital image processing. Focal myocardial enhancement on spin echo MRI strongly supports a diagnosis of myocarditis, especially when associated with regional wall motion abnormalities [40•]. Echocardiography, the most readily available diagnostic modality, may help differentiate acute and fulminant myocarditis. Patients with fulminant myocarditis had near normal left ventricular diastolic dimensions but increased septal thickness when compared with patients with acute myocarditis who had increased diastolic dimensions but normal septal wall thickness [41•].

### Treatment

The treatment of myocarditis has improved significantly over the last decade (Table 3). However, supportive

**Table 2. Diagnostic modalities for myocarditis**

Clinical symptoms
Clinical heart failure, recent flulike syndrome, arrhythmias
Invasive
Myocardial biopsy—histological characteristics (Dallas criteria)*,
PCR
Serological
Creatinine kinase, troponin I, troponin T, aFas, sFasL, CRP, tracheal
aspirate PCR, leukocytosis, sedimentation rate, autoantibodies
(anti-adenine nucleotide translocator, antimyosin) eosinophilia,
TNF- $\alpha$
Noninvasive
Atinmyosin scintigraphy, contrast-enhanced MRI, echocardiography
and echocardiographic digital image processing, cine magnetic
resonance angiography, electrocardiogram

care is still the mainstay of therapy for patients with myocarditis. Patients with symptomatic heart failure should be treated with conventional heart failure medications including angiotensin converting enzyme inhibitors, digitalis, diuretics, and, after stabilization, beta-blockers. New evidence suggests a potential downside to using digoxin. In a murine model of viral myocarditis, researchers found increased expression of proinflammatory cytokines and increased mortality in animals treated with high-dose digitalis [42]. Digoxin should, therefore, be used with caution and at low doses. Coxsackievirus B3 may be associated with alterations in trace elements in the infected myocardium, therefore, rhythm must be closely monitored. An increase in intracellular calcium and decrease in magnesium may contribute to increased risk of arrhythmias [43].

The use of immunosuppression in patients with myocarditis remains controversial. Intravenous immunoglobulin therapy may suppress myocarditis by immunomodulation and the reduction of neurohumoral activity. A recent study in the murine myocarditis model showed that intravenous immunoglobulin administration ameliorated both myocardial necrosis and interstitial fibrin deposition by the reduction of plasma catecholamines, interferon-alpha, and soluble intercellular adhesion molecule-1 [44•]. Other immunosuppressive agents that have been used in patients with acute myocarditis and severe heart failure include methylprednisolone, cyclosporine, azathioprine, and OKT3. The use of OKT3 in the immunosuppressive regimen was shown to inhibit or reverse immune response and dramatically improve myocardial function [45]. This retrospective study, like most reports of immunosuppression in myocarditis, was uncontrolled, nonrandomized and limited by its small sample size and inability to specifically isolate the effect of OKT3 on myocarditis. The antigen-presenting cells in the heart that are required for the effector T cells to cause autoimmune myocarditis are a dynamic bone marrow-derived population and not a fixed popu-

lation [20•]. This may raise the possibility of myelosuppression as a treatment modality in acute myocarditis. In general, there is insufficient convincing evidence of therapeutic benefit to recommend the routine use of immunosuppression for acute myocarditis. The ongoing European Trial may provide evidence for a role for immunosuppression [32].

Delivery of antigens by the nasal route can induce antigen-specific tolerance and suppress certain autoimmune diseases. Nasal administration of cardiac myosin in the mouse was associated with decreased severity of myocarditis [46•]. Clinical application of potential therapies using antigenic tolerance, however, remains premature at present. The identification of specific receptor proteins to which cardiotropic viruses may bind raises the potential for blocking these receptors, thereby preventing myocellular injury during viral infection. Initial animal experiments have demonstrated resistance to viral infection when the CAR antigen was blocked by specific monoclonal antibodies [47]. As new evidence points to the persistence of viral RNA beyond the acute phase and its possible role in the evolution to dilated cardiomyopathy, use of antiviral medications needs to be investigated. Several recent case reports have documented successful treatment of myocarditis with antiviral agents [48,49]. Antiviral therapy is being assessed in ESETCID, in which study enterovirus-positive patients are randomly assigned to treatment with the antiviral agent interferon- $\alpha$  or placebo [50]. Because coxsackievirus protease 2A release leads to myocardial cytoskeleton damage and dilated cardiomyopathy, protease inhibitors may be reasonable agents to consider for clinical investigation.

Patients with rapidly progressing severe heart failure and shock may benefit from mechanical cardiac support with a left ventricular assist device (LVAD), biventricular assist device (BVAD) or extracorporeal membrane oxygenation (ECMO). LVAD or ECMO can be an effective bridge to transplantation in patients with fulminant heart failure (B. Duncan, MD, written communication, February 2000) [51]. However, the currently available LVAD and ECMO systems are not suitable for extended support in the pediatric population. Cardiac transplantation should be considered in all patients with acute myocarditis and severe heart failure. However, patients with fulminant myocarditis who have severe heart failure may have a good long-term prognosis and should be given sufficient time to demonstrate recovery and not be rushed to heart transplant [11••].

## Prognosis

It is difficult to say what the exact prognosis of the entire spectrum of acute myocarditis is, because patients with subclinical myocarditis may have only mild symptoms and may go undetected. Conventional prognostic estimates

**Table 3. Therapy for myocarditis**

Standard therapy
ACE inhibitors, digitalis, diuretics, beta-blockers
Immunosuppression
IVIG, steroids, azathioprine, cyclosporine, cytoxan, OKT3
Mechanical support
LVAD, BVAD, ECMO
Novel therapy
Myelosuppression, viral vaccination, antiviral agents, protease inhibitors, specific monoclonal antibodies blocking the CAR antigen
Rescue therapy
Heart transplant

ACE, angiotensin-converting enzyme; BVAD, biventricular assist device; CAR, coxsackie-adenovirus receptor; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; OKT3.

are that one third of patients recover and do well, one third improve clinically but have residual myocardial dysfunction, and one third do poorly and have chronic heart failure, which may cause mortality or require heart transplantation. Severity at onset does not necessarily predict long term survival. A recent report of 132 adult patients with biopsy-proven acute myocarditis showed a 45% survival at 11 years. This was in sharp contrast to a 93% survival without transplant in 15 patients with fulminant myocarditis [11••]. Patients with both acute and fulminant myocarditis presented with similar degrees of myocardial dysfunction (shortening fraction [SF]  $19 \pm 4\%$  vs  $17 \pm 7\%$ ). However at 6 months follow-up, patients with fulminant myocarditis had undergone dramatic improvement in left ventricular function (SF =  $30 \pm 8\%$ ) compared with no significant improvement in patients with acute myocarditis [41•]. Children at three North American centers, who required mechanical circulatory support for severe, acute myocarditis, had a survival rate of 80% at 1 year (B. Duncan, MD, written communication, February 2000). Conversely, giant cell myocarditis is a highly lethal disorder characterized by rapidly progressive congestive heart failure. The prognosis of giant cell myocarditis is especially poor, with approximately 70% of patients having died or been transplanted at 1 year [52•]. In contrast to the above encouraging results with mechanical cardiovascular support, patients with giant cell myocarditis who required an LVAD before transplantation had only a 29% 1-year posttransplant survival rate. Patients who did not require LVAD had a 93% 1-year posttransplant survival [53].

## Conclusions

New information continues to emerge to help us better understand the causes, pathogenesis, diagnosis, and treatment of myocarditis. The prognosis of patients with myocarditis has improved significantly over the last decade, particularly since the advent of improved therapy for heart failure and the introduction of mechanical cardiovascular support. Treatment modalities targeting cytokines and hormonal receptors, antiviral modalities including vaccination, and better and longer lasting assist devices are on the horizon. With such progress, we should be able to better diagnose and treat patients with myocarditis and mitigate dilated cardiomyopathy as a long-term sequela of acute myocarditis.

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