Etiology and pathogenesis of myocarditis

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INTRODUCTION — Myocarditis is an inflammatory disease of cardiac muscle, diagnosed on endomyocardial biopsy (EMB) by established histological, immunological, and immunohistochemical criteria [1]. It can be acute, subacute, or chronic, and there may be either focal or diffuse involvement of the myocardium. In symptomatic patients, the cardiac presentation is frequently one of acute heart failure (HF), although a syndrome mimicking acute myocardial infarction or a tachyarrhythmia, including sudden death, or high-grade heart block may occur. If the epicardium is involved, pericarditis may be associated with pleuritic chest pain and pericardial effusion. Isolated endomyocardial inflammation and fibrosis is seen in Löeffler's cardiomyopathy, tropical endomyocarditis, hypereosinophilic syndrome, and some adverse drug reactions.

The etiology and pathogenesis of myocarditis will be reviewed here. Issues related to the clinical manifestations, diagnosis, natural history, and treatment of myocarditis are discussed separately. (See "Clinical manifestations and diagnosis of myocarditis in adults" and "Treatment and prognosis of myocarditis in adults".)

ETIOLOGY — Myocarditis can be caused by a variety of infectious and noninfectious illnesses (table 1). Among the infectious etiologies, viruses are the presumed most frequent pathogens, but bacteria, fungi, protozoa, and helminths have also been implicated [2,3]. In North America and Western Europe, the most frequently identified viruses were enteroviruses (including coxsackievirus) until the 1990s. Parvovirus B-19 and human herpes virus 6 are the viruses most frequently found.

This topic review will focus on viral and hypersensitivity myocarditis. Many of the other causes of myocarditis are discussed in detail elsewhere in UpToDate. These include:

- Infections such as acute rheumatic fever due to group A streptococci and Chagas disease. (See "Epidemiology and pathogenesis of acute rheumatic fever" and "Chagas heart disease: Clinical manifestations and diagnosis".)
- Autoimmune disorders such as systemic lupus erythematosus, Wegener's granulomatosis, giant cell arteritis, and Takayasu arteritis [4-6]. Among patients with lupus, myocarditis has been clinically suspected in approximately 9 percent of cases, including approximately 6 percent with global hypokinesis on echocardiography [4]. Postmortem studies have suggested that the majority of patients dying of lupus have myocardial involvement. (See "Non-coronary cardiac manifestations of systemic lupus erythematosus in adults", section on 'Myocarditis'.)
- Drug reactions, including cocaine abuse, that may be overlooked in the differential diagnosis [7,8]. (See "Evaluation and management of the cardiovascular complications of cocaine abuse".)

Viral or "idiopathic" myocarditis — Viral infection is the most commonly identified cause of lymphocytic myocarditis [9,10]. In the 1960s, a link was suggested by seroepidemiologic studies between enterviral infection, particularly coxsackievirus, and human myocarditis [11]. Since that time, about 20 viruses have been implicated in human myocarditis (table 1). Molecular techniques, such as polymerase chain reaction (PCR) and in situ hybridization, have permitted the direct detection of viral genomes in the hearts of patients with acute myocarditis and dilated cardiomyopathy [12,13].

Pathogen — Viral infection is commonly associated with myocarditis in series from Western Europe and North America. The most frequently implicated viruses in the 1980s and 1990s were Coxsackie B virus [10,12,14-16], adenovirus [12,16], hepatitis C [17], cytomegalovirus (CMV) [12,18,19], echovirus [16], influenza virus [12], Epstein-Barr virus (EBV) [12,20], and the viruses of childhood exanthematous diseases, including parvovirus B19 [2,12,16,21-23]. The most common viral genomes identified in patients with suspected myocarditis are human herpes virus 6 and parvovirus B19 [13,24,25]. Enterovirus still causes myocarditis in small regional outbreaks. H1N1 influenza A infection may cause fulminant myocarditis [26]. (See "Clinical manifestations and diagnosis of pandemic H1N1 influenza ('swine influenza').")

Vaccinia virus inoculation for protection against smallpox infection results in myocarditis with or without associated pericarditis in approximately 1.2 per 10,000 military vaccinees and 6 per 10,000 civilian vaccinees [27,28]. In the civilian vaccination program, the incidence of myocarditis with or without associated pericarditis was 1.3 per 10,000 vaccinees if only probable cases are included and 5.5 per 10,000 vaccinees if suspected cases are included [29]. The lower rate in
military vaccinees could reflect a highly selected fit population without underlying disease. (See "Vaccinia virus as the smallpox vaccine", section on 'Myocarditis and myopericarditis'.)

The relative frequency and type of viral infection as a cause of myocarditis was best evaluated in a large multicenter series of patients with biopsy-proven myocarditis [12]. The study included 624 patients, age 1 day to 42 years (mean 6.2 years), with acute HF or cardiovascular collapse and an endomyocardial biopsy (EMB) positive for myocarditis by the Dallas criteria. (See "Clinical manifestations and diagnosis of myocarditis in adults", section on 'Dallas criteria'.)

Cultures were obtained from blood, urine, stool, nasopharynx, and EMB specimens. Serial serologies were obtained, and PCR was performed on blood and cardiac tissue to identify viral nucleic acid. An additional 149 patients had acute HF with a negative EMB and were diagnosed with new onset dilated cardiomyopathy (DCM); 165 control patients with other cardiac disorders were also evaluated. The following observations were made:

- Serology, cultures, and PCR (of cardiac tissue) each detected a viral pathogen in approximately one-third of myocarditis patients; PCR detected a pathogen in 20 percent of DCM patients and only 1.4 percent of controls. Blood samples were positive by PCR in only 1 percent.
- In case series, parvovirus 19 has been commonly detected by PCR from myocardial biopsy specimens in patients with acute and chronic dilated cardiomyopathy [13,21,30].

The PCR findings should not be interpreted as providing a definitive diagnosis of the cause of myocarditis cases, since intercurrent or previous viral infection unrelated to the episode of myocarditis cannot be ruled out [12]. Furthermore, among patients who had both positive peripheral cultures and a positive PCR, the results were in agreement in only 76 percent of cases. Despite these concerns, these data suggest that viral pathogens are commonly associated with histologic evidence of myocarditis.

**Incidence and prevalence** — The true incidence of idiopathic or "viral" myocarditis in the general population is unknown. In early studies, cardiac involvement was suspected to occur in 3.5 to 5 percent of patients during outbreaks of Coxsackievirus infection [14,31,32]. However, there is significant difficulty in establishing a diagnosis of myocarditis because EMB, the diagnostic reference technique, is infrequently used and there is no established noninvasive "gold standard." Furthermore, the sensitivity of EMB, which may reveal a lymphocytic infiltrate, sometimes with evidence of myocardial damage, may be as low as 35 percent by conventional histology (Dallas criteria), although immunohistochemistry and viral PCR have yielded higher sensitivity [12,13,16,20,23,30]. (See "Clinical manifestations and diagnosis of myocarditis in adults", section on 'Endomyocardial biopsy'.)

Autopsy studies have revealed varying estimates on the incidence of myocarditis that vary with the population studied. In a registry of 1866 young athletes who died suddenly, 6 percent had myocarditis [33]. A 5 percent prevalence of active myocarditis was reported in a high-risk group of 186 sudden, unexpected medical deaths in children [34]. A similar incidence was noted among traumatic deaths in British males aged 18 to 55 years; in this setting, the myocarditis was asymptomatic [35].

Other reports have evaluated the prevalence of myocarditis as a cause of initially unexplained DCM. In a review of 1230 such patients, myocarditis as defined by the Dallas criteria was felt to be responsible in 9 percent [36], and myocarditis was identified in 10 percent in the over 2200 patients with unexplained HF of less than two years duration in the Myocarditis Treatment Trial [37].

Certain groups appear to be at increased risk for fulminant viral myocarditis. As an example, children, especially neonates and those who are immunocompromised, may have a severe illness with hemodynamic compromise. In one series, lymphocytic myocarditis was present in 25 of 62 children with dilated cardiomyopathy (40 percent) who underwent cardiac histologic examination within two months of presentation with dilated cardiomyopathy [38].

**Protective effect of initial immune response** — By age 30, between 18 and 94 percent of people have antibodies to one or more coxsackie B virus serotypes [39-41]. It is likely that this humoral response soon after infection is beneficial, acting to decrease inflammation.

Compatible with the beneficial effect of the initial immune response is the observation from the Myocarditis Treatment Trial Investigators that findings consistent with a stronger humoral and cellular immune response were associated with less severe initial disease [37]. Supporting this concept, immune deficient mice develop a severe myocarditis between 7 and 14 days after inoculation with a high subsequent mortality [42].
Among the factors that may be protective in the initial immune response are regulatory T cells [43], natural killer (NK) cells [44], nitric oxide [45], and interferon beta and interferon gamma [46-48]. In a transgenic mouse model in which the pancreatic beta cells express interferon gamma, the spread of an infecting virus is reduced, and infection with coxsackievirus B3 does not produce myocarditis as it does in normal mice [46]. In a mouse strain lacking the interferon beta gene, susceptibility to coxsackievirus B3 is increased [47]. (See Role of cytokines below.)

These data, which come almost entirely from animal models, suggest the importance of reducing the level of viremia early during infection. If, however, the initial immune response is insufficient, persisting and possibly replication deficient viruses may drive an adverse autoimmune immune response or directly cause myocyte damage (see 'Autoimmune mechanisms' below).

**Giant cell myocarditis** — Idiopathic giant cell myocarditis is a rare, severe, virus-negative, and frequently fatal type of autoimmune myocarditis that may respond to immunosuppressive therapy [49]. In an animal model, a disorder similar to giant cell myocarditis was induced by immunization with cardiac myosin [50]. In this model, myocardial damage is primarily mediated by T lymphocytes. (See "Treatment and prognosis of myocarditis in adults", section on 'Giant cell myocarditis'.)

**Hypersensitivity myocarditis** — Hypersensitivity myocarditis (HSM, a form of eosinophilic myocarditis) is an autoimmune reaction in the heart that is often drug-related and is usually characterized by acute rash, fever, peripheral eosinophilia, and ECG abnormalities such as nonspecific ST segment changes or infarct patterns [51,52]. However, some patients present with sudden death or rapidly progressive HF. The true incidence of HSM is unknown. One estimate comes from an autopsy study, which identified 16 cases in more than three thousand consecutive autopsies (<0.5 percent) [52]. In other series, the prevalence of clinically undetected HSM in explanted hearts ranged from 2.4 to 7 percent [53].

HSM is usually temporally related to a recently initiated medication. Numerous drugs have been implicated in this drug-induced hypersensitivity syndrome, including methyl dopa, hydrochlorothiazide, furosemide, ampicillin, tetracycline, azithromycin, aminophylline, phenytoin, benzodiazepines, and tricyclic antidepressants [54-56]. However, HSM does not always develop early in the course of drug use. As an example, patients taking the antipsychotic agent clozapine have been reported to develop myocarditis more than two years after the drug was started [57]. (See "Drug allergy: Pathogenesis".)

Eosinophilic myocarditis has also been seen in 2.4 to 23 percent of patients treated with dobutamine infusion [58-62]. It is uncertain whether this reaction represents hypersensitivity to the drug itself or a reaction to sodium bisulfite, which is a preservative in many dobutamine preparations [58,60]. It has been diagnosed either on EMB or retrospectively after explantation of the native heart. In some cases, tapering or discontinuation of dobutamine infusion has resulted in diminution of the peripheral eosinophilia and histologic improvement [60].

Histologically, HSM is usually characterized by an interstitial infiltrate with prominent eosinophils, but little myocyte necrosis [52]. However, occasional patients with apparent drug hypersensitivity have giant cell myocarditis, granulomatous myocarditis, or necrotizing eosinophilic myocarditis [63,64]. These disorders can usually be distinguished from hypersensitivity myocarditis only by EMB. (See "Treatment and prognosis of myocarditis in adults", section on 'Eosinophilic myocarditis'.)

**Celiac disease** — Two reports from Italy suggest that celiac disease, which is often clinically unsuspected, accounts for as many as 5 percent of patients with autoimmune myocarditis or idiopathic DCM [65,66]. In one review, 187 consecutive patients with myocarditis were screened for IgA antiendomysial and anti-tissue transglutaminase antibodies; patients with a positive test underwent duodenal endoscopy and biopsy [65]. (See "Diagnosis of celiac disease in adults".)

The following findings were noted:

- Nine patients (4.8 percent) had celiac disease, compared to 1 of 306 controls (0.3 percent). All nine had anti-heart antibodies in the serum.
- None of these patients had classic gastrointestinal symptoms of celiac disease (recurrent abdominal pain, diarrhea, and weight loss), but all had iron deficiency anemia that was refractory to iron replacement.
- Four patients with ventricular arrhythmia and normal cardiac function improved with a gluten-free diet alone. Five patients had progressive HF that failed to respond to more than six months of conventional HF therapy; they were then treated with immunosuppression and a gluten-free diet with a marked improvement in symptoms and left...
ventricular ejection fraction (LVEF; absolute 18 to 35 percent increase). Although spontaneous improvement is common in patients with myocarditis, these patients had failed a prolonged course of standard therapy.

In a study of 45 children with celiac disease, subclinical systolic dysfunction was present in those children who had high titers of antiendomysial antibodies [67]. Autoimmune disorders occur with increased frequency in patients with celiac disease and may be related in part to antigen overload resulting from increased intestinal permeability. (See "Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults").

Although these findings are intriguing, it would be premature to screen all patients with otherwise unexplained myocarditis for celiac disease. However, it is reasonable to ask about a history of gastrointestinal complaints or refractory iron deficiency.

Arrhythmogenic RV cardiomyopathy — Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an unusual clinical entity characterized by ventricular arrhythmias and a specific right ventricular (RV) pathology. ARVC is associated with a fatty appearance of the RV free wall; the fibrofatty replacement of the RV myocardium initially produces typical regional RV paradoxical wall motion abnormalities, which later become global, producing RV dilation. The condition is often familial. (See "Arrhythmogenic right ventricular cardiomyopathy: Anatomy, histology, pathogenesis, and genetics" and "Clinical manifestations and diagnosis of arrhythmogenic right ventricular cardiomyopathy").

It has been suggested that some patients with anatomic features of ARVC and no family history of ARVC have myocarditis. In one report, 30 patients without a family history of ARVC with ventricular arrhythmias, evidence of either global or regional RV dysfunction, and diagnostic criteria for ARVC underwent extensive RV and LV biopsies [68]. Focal inflammatory infiltrates with necrosis of adjacent myocytes, meeting the Dallas criteria for myocarditis, were present in 21 (70 percent).

Hypertrophic cardiomyopathy — Histologic findings compatible with myocarditis can occur in patients with hypertrophic cardiomyopathy and have been associated with rapid deterioration in LV systolic performance; viral genomes have been identified in some of these patients [69].

Vaccinia-related myopericarditis — Vaccinia-related clinically suspected myocarditis and/or pericarditis is a complication of smallpox vaccination and is discussed separately. (See "Myopericarditis").

VIRAL MYOCARDITIS AND DILATED CARDIOMYOPATHY — The role of viral myocarditis in DCM is an important clinical issue. There are several potential mechanisms by which a viral myocarditis might cause acute or chronic DCM, including direct viral damage or as a result of humoral or cellular immune responses to persistent viral infection.

Direct viral injury — Our understanding of the pathogenesis of viral myocarditis comes almost entirely from experimental models of acute coxsackie B virus infection [70]. The initial change is myocyte damage in the absence of a cellular immune response. The myocyte injury may be mediated through direct viral toxicity, perforin-mediated cell lysis, and cytokine expression [71].

Intracellular events — Viral entry into the myocyte is mediated by cell surface receptors. The coxsackie-adenovirus receptor (CAR) is a common receptor for coxsackievirus type B and for adenovirus subgroups A, C, D, E, and F [72-74]. The CAR gene has been localized to chromosome 21q11.2 [75]. With rare exceptions, CAR expression is required for virus entry into cells.

The discovery of the CAR receptor raises the possibility of interventional therapy to block CAR in severe cases of coxsackie B virus or adenoviral myocarditis. Coreceptors, including decay-accelerating factor (DAF, CD55) for some coxsackie B virus strains [76] and integrins, help determine the efficiency of infection [77,78]. The activity of signaling pathways in cardiac myocytes also may determine susceptibility to coxsackie B myocarditis via effects on viral replication [79].

After entry into the cell through the CAR receptor, the coxsackie B viral genome is translated into structural capsid proteins and several proteases that cleave the viral polyprotein. Viral protease 2A can also cleave certain host proteins, and one mechanism of ongoing myocyte injury is through direct interaction of viral proteins with the cytoskeleton. In a transgenic mouse model, cardiac-restricted expression of protease 2A was sufficient to induce dilated cardiomyopathy [80].

Protease 2A cleaves dystrophin in vivo, leading to disruption of the dystrophin-glycoprotein complex that is essential for normal cardiac function [81]. Disruption of the dystrophin-glycoprotein complex is also present in hereditary cardiomyopathies that are related to a dystrophin mutation, such as Duchenne muscular dystrophy [82].
features and diagnosis of Duchenne and Becker muscular dystrophy). There is more efficient release of the coxsackie B virus from dystrophin-deficient cells [83]. Thus, dystrophin-deficient mice have greater viral replication and more severe cardiomyopathy.

**Persistent viral infection**—As noted above, the initial immune response plays a protective role against the development of coxsackie B myocarditis. The possible importance of persistent viral replication was illustrated in a study of coxsackie B virus myocarditis in immunocompetent mouse strains [84]. Entero viral RNA was present in acute myocarditis and persisted during the chronic phase of cardiomyopathy.

Subsequent studies showed that persistent viral infection was associated with myocardial dysfunction [85,86]. In a transgenic mouse model, for example, the expression of coxsackievirus DNA and the synthesis of viral RNA without formation of infectious viral progeny resulted in typical morphologic features of a human DCM [86]. The isolated myocytes had defective excitation-contraction coupling and a decrease in shortening.

Serologic testing, PCR, and probe hybridization in humans have strengthened the connection between persistent myocardial viral infection and the development of DCM [12,16,87,88]. Adenovirus and enterovirus were the most commonly identified viruses in the 1990s. In later studies, parvovirus B-19 and human herpesvirus 6 have been identified more frequently [12,13,25,89-93]. In addition, many other viruses have been implicated including HIV, hepatitis C, cytomegalovirus, and varicella [13,25,94-97]. (See ‘Pathogen’ above.)

Indirect support for a pathogenetic role of persistent viral infection was provided in a report cited above of 172 consecutive patients with viral infection of the myocardium by PCR [16]. The LVEF increased in the one-third of patients who had spontaneous clearance of the viral genome on follow-up biopsy at a median of 6.8 months (58 versus 50 percent); in contrast, the LVEF fell in the remaining patients with persistence of the viral genome (54 versus 51 percent).

**Enterovirus**—The possible role of persistent entero viral infection in the development of DCM can be illustrated by the following findings:

- In the large multicenter series of patients with myocarditis cited above, 149 had a negative biopsy and were diagnosed with new onset DCM [12]. Of these, 12 were positive for enterovirus by PCR (8 percent). Of the 215 controls (no DCM), only one was positive for enterovirus (0.5 percent).
- In an early series of 45 patients with left ventricular (LV) dysfunction and clinically suspected myocarditis, 22 percent had active entero viral RNA replication in the myocardium; in comparison, entero viral RNA was not found in any of the biopsies from 26 controls [91].
- In a prospective evaluation of 120 patients with myocarditis or idiopathic DCM, entero viral RNA sequences were detected in 34 percent [92]. At two years, mortality was significantly increased in the enterovirus-positive patients (25 versus 4 percent in the enterovirus negative group). However, conflicting prognostic data were noted in another report in which mortality at two years in patients with DCM was significantly lower in those who were enterovirus-positive (5 versus 19 percent) [98]. In another study, the presence of viral genome was not related to outcome [13].

**Adenovirus**—Adenoviruses, which were frequently present in children with cardiomyopathy in the 1980s and 90s [99], are now less common in children and adults [90]. A review of 94 adults with idiopathic DCM and 14 controls detected adenoviral type 2 genomic DNA in 13 percent and entero viral RNA in another 13 percent [89]. All control samples were negative for both viruses. In two later series, adenovirus was an uncommon pathogen in adult with biopsy-proven myocarditis [13,30] or dilated cardiomyopathy [13].

**HIV**—DCM, occasionally due to myocarditis, develops frequently in advanced HIV infection and is associated with poor prognosis. DCM in HIV may be caused by toxicity of the gp120 protein, adverse reaction to antiviral agents, or to opportunistic infections [95,100]. HIV rarely infects cardiac myocytes, and current opinion is that direct HIV cardiotoxicity is uncommon. Myocarditis was found in 6 of 14 (44 percent) heart biopsies from patients with HIV who had an average CD4 count of 246 and who were not treated with highly active antiretroviral therapy. The most common viruses identified were EBV and HSV [101]. (See "Cardiac and vascular disease in HIV-infected patients", section on ‘Myocardial disease’.)

**Hepatitis C**—Hepatitis C virus (HCV) infection has been proposed to be associated with myocarditis and a cardiomyopathy in Japan. A multicenter study of 697 Japanese patients found that HCV antibody was present in 10.6 percent of patients with hypertrophic cardiomyopathy, 6.3 percent with a DCM, and 2.4 percent of normal controls [96]. These data suggest that HCV infection may be associated with hypertrophic cardiomyopathy in the Japanese population. Studies to determine the association with HCV infection in populations from North America and Western Europe are lacking. Independent confirmation of these intriguing observations is needed. HCV is not an established cardiotropic virus
and it is not known how it might cause a cardiomyopathy. In an animal model, mice that were transgenic for the HCV core gene developed a cardiomyopathy by 12 months [102]. This observation suggests a possible pathogenetic role for HCV core protein.

**Other** — In contrast to the above report that evaluated specific viruses as a cause of DCM, one study performed PCR analysis for multiple viral genomes on EMB from 245 patients with idiopathic DCM, none of whom had evidence of active or borderline myocarditis [103]. Viral genomes were identified in 67 percent, including 27 percent with multiple infections. The most common viruses isolated were parvovirus B19 (51 percent), human herpesvirus-6 (22 percent), enterovirus (9 percent), and Epstein-Barr virus, adenovirus, and cytomegalovirus, each of which was present in ≤2 percent of biopsies. Parvovirus B19 viral genomes have also been associated with idiopathic left ventricular diastolic dysfunction [104].

**Autoimmune mechanisms** — Autoimmune mechanisms have been implicated in the pathogenesis of myocarditis, with or without a virus trigger. A subset of patients with biopsy-proven virus-negative myocarditis fulfill the Witebsky-Rose criteria for an autoimmune disease [10,30,49,50,65,66,105]. Autoimmune myocarditis may occur in isolation or in the context of extra-cardiac autoimmune disorders, eg SLE [4]. Autoimmunity may also account for 30 to 40 percent of patients with idiopathic dilated cardiomyopathy [105]. (See "Causes of dilated cardiomyopathy", section on 'Autoimmunity'.)

In patients with viral myocarditis, the initial immune response limits the degree of viremia early during infection and protects against myocarditis. (See 'Protective effect of initial immune response' above.) If, however, this response is insufficient, the virus may not be eliminated and further myocyte injury may ensue. In addition to direct viral-induced injury, persisting viral genomic fragments that may not be capable of replicating as intact virus may drive an adverse autoimmune response (figure 1) [106]. However, in genetically predisposed experimental models and in patients, autoimmune inflammatory heart disease may develop in the absence of a defined previous viral myocarditis.

Potentially pathogenic autoantibodies to a variety of cellular components are found in a high percentage of patients with myocarditis and DCM. Autoantigens include alpha and beta cardiac myosin heavy chain, the beta-1 adrenoreceptor, adenine nucleotide translocator (ANT), branched chain keto acid dehydrogenase (BCKD), a variety of sarcolemmal and myolemmal proteins, connective tissue, and extracellular matrix proteins, including laminin [107-115].

The pathogenesis of anti-heart antibodies in post-viral autoimmune cases may start with direct viral-induced myocyte damage, with associated release of intracellular proteins. Intracellular antigens may be recognized as foreign because they were previously sequestered from immune surveillance or through molecular mimicry between enteroviral proteins and cardiac proteins. CD4-positive T cells produce myocyte damage by stimulating B cells, cytotoxic cytokines, and cytotoxic CD8+ T cells. The presence of the organ and disease-specific anti-heart autoantibodies of IgG class detected by indirect immunofluorescence on human heart predicts the subsequent development of DCM or left ventricular dysfunction in relatives of patients with DCM from both familial and nonfamilial pedigrees [116].

The subclass of immunoglobulin may be important in antibody-mediated DCM. In one study of 82 DCM patients, levels of immunoglobulin subclass IgG3, but not IgG1 or IgG2, were elevated compared to controls [117]. In another report of 76 patients with clinically suspected myocarditis or DCM, there was a significant correlation between the plasma concentration of IgG3 and both hemodynamic and echocardiographic indices of HF severity [118].

The role of IgG3 may have implications for therapy. Immunoabsorption for the removal of autoantibodies may be performed either with protein A columns (which bind to and remove most IgG, but have a low affinity for IgG3), or with anti-IgG columns (which have specificity for all IgG subclasses). In a trial in which the two types of columns were compared for the monthly treatment of DCM, only the anti-IgG column was associated with significant improvement in cardiac index with the first treatment and at three months [119]. The benefit may be increased with more efficient IgG3 removal [120]. (See "Investigational and emerging therapies for heart failure", section on 'Immunoabsorption'.)

**Anti-alpha myosin antibodies** — The potential importance of anti-alpha myosin antibodies has been illustrated in several reports. In one study of 53 patients with clinical myocarditis, for example, 17 percent had anti-alpha myosin antibodies, compared to only 4 percent of patients with ischemic heart disease and 2 percent of normal controls [108].

In another series of 33 patients, anti-alpha myosin antibodies were present in 17 [109]. The antibodies persisted in the majority of patients for at least six months, and did not develop in any patient after the diagnosis of clinical myocarditis had been made. The presence of anti-alpha myosin antibodies was associated with a lower likelihood of improvement in LV systolic and diastolic function at six months compared to patients without these antibodies (no increase in LVEF
Anti-beta-1 adrenocortceptor antibodies — Anti-beta-1 adrenocortceptor antibodies also may play a role in the progression of myocarditis to DCM. In a rabbit model, immunization with sequences of the beta-1 adrenocortceptor results in the production of anti-beta-1 adrenocortceptor antibodies and the development of a cardiomyopathy that resembles the human idiopathic disease [110]. These findings appear to be applicable to humans since these autoantibodies can be detected in as many as 38 percent of patients with an idiopathic DCM [111,112].

Removal of anti-beta-1 adrenocortceptor antibodies by selective immunoabsorption has been associated with clinical improvement in patients with idiopathic DCM [112,113]. (See "Causes of dilated cardiomyopathy", section on 'Autoimmunity'.)

In addition to promoting myocardial injury, one subgroup of these autoantibodies, directed at the second extracellular domain of the beta-1 adrenocortceptor, exerts agonist-like activity on the beta adrenocortceptor and may play a role in the development of serious ventricular arrhythmias [111]. (See "Pathogenesis of ventricular arrhythmias in heart failure and cardiomyopathy").

Autoreactive T cells — Cellular immunity also may be involved in the development of a DCM. This was suggested in a study that evaluated myocardial, lymph node, and thymic tissue samples from patients with idiopathic DCM [121]. Overexpression of activated helper and cytotoxic T cells was associated with the presence of coxsackie B virus, which may have been the trigger for a superantigen-mediated immune response (figure 1).

In animal models, cellular immunity is a major mechanism of myocardial injury in post-coxsackie B virus myocarditis [122,123]. This was illustrated in a study in which genetically susceptible mice were crossed with knockout mice lacking CD4+ and/or CD8+ T cells [122]. There was a small decrease in inflammatory infiltrate at 14 days after coxsackie B virus inoculation in mice that lacked CD4+ T cells and a major decrease in mice that lacked both CD4+ and CD8+ T cells. In addition to Th1 and Th2 T cell-mediated myocardial injury, Th17 positive T cells, a T cell subtype that releases IL-17, can mediate autoimmune myocarditis. The Th17 pathway is interesting, since it can be selectively blocked without affecting neutrophil activation [124]. In experimental myocarditis, differentiated CD4+ T cells may change their functional program from Th17 to T regulatory cells under certain cytokine environments, altering the types of cytokines they produce [125].

Role of cytokines — In the postviral setting, cytokines regulate lymphocyte function in a positive and negative manner and exert a marked influence on the activities of many other cell types engaged in tissue repair and restoration of homeostasis. (See "Role of cytokines in rheumatic diseases").

In animal models, progression from myocarditis to a DCM is characterized by a change in cytokine expression [126]. Th1 cytokines, including interleukin (IL)-2, interferon gamma, and IL-1-beta, are expressed early in the lesions [127]. The transition to fibrosis and a DCM is heralded by a decrease in the Th1 cytokines and an increase in IL-10, a Th2 cytokine. Gene transfer of IL-10 can protect against autoimmune myocarditis in rats, probably by suppressing the early Th1 type response [128]. However, in one study of patients with myocarditis of unspecified etiology, higher serum levels of IL-10 were associated with greater disease severity and higher mortality [129].

Tumor necrosis factor-alpha (TNFa) has been implicated in the pathogenesis of myocarditis and DCM in a few animal and human studies [130]. (See "Nitric oxide, other hormones, cytokines, and chemokines in heart failure"). Support for the role of TNFa in myocarditis comes from a study of transgenic mice with myocardial expression of TNFa [131]. Production of this cytokine by cardiac myocytes was sufficient to cause severe cardiac disease, including transmural myocarditis and ultimately biventricular fibrosis, chamber dilatation, and LV dysfunction. In addition, there is a strong linear relationship between mortality and TNFa levels in a mouse model of HF due to viral myocarditis [132].

In human myocarditis, endomyocardial biopsy specimens show higher levels of a TNFa precursor and the TNFa converting enzyme (TACE), which converts the precursor to its mature form within the myocytes and interstitial cells [133]. TACE and TNFa expression were greater in patients with NYHA class III and IV HF than in those in NYHA class I and II, and increased expression was correlated positively with LV volume and negatively with LV systolic function. However, the clinical importance of TNFa in DCM remains uncertain as randomized trials of anti-TNFa therapy have failed to show benefit. Cytokine expression profiles should be studied in human myocarditis/DCM of defined viral versus autoimmune pathogenesis prior to translating results from experimental models to the clinical arena.

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●Basics topics (see "Patient information: Myocarditis (The Basics)"

Summary

●Viral injury and post-viral autoimmune response may be simplified into a three-phase model to characterize the stages of the progression of acute viral infection to DCM; the acute viral myocarditis and autoimmune models of myocarditis/DCM development are depicted in the figure ([Figure 1]). The two models do not exclude each other, and may account for the progression from myocarditis to DCM in distinct patient subsets [134].

• The first phase is comprised of viral infection with myocyte death within hours of viral cell entry. In this acute stage, myocyte death results from direct viral damage to myocytes and leads to exposure of host proteins to the immune system.

• The second phase, which rapidly follows, is an innate immune response comprised of altered regulatory T cell function, NK cells, interferon gamma, and nitric oxide.

• In the third phase, a virus-specific immune response includes antibodies to pathogen. Non-genetically susceptible animals and humans recover with few consequences. In genetically susceptible experimental animals and humans, a breakdown of T cell tolerance to self myocardial autoantigens (eg, cardiac myosin) ensues. This leads to chronic myocardial inflammation, necrosis/apoptosis, and fibrosis mediated by humoral (Autoantibody-mediated) and/or cell-mediated organ-specific autoimmunity. These patients may die from arrhythmias or progress onto a phase of DCM with chronic heart failure.

● In genetically predisposed animals and humans, a long asymptomatic latency period, characterized by ongoing myocardial tissue inflammation and damage, resulting in detectable markers of immune activation in situ (inflammatory cells, increased HLA, and adhesion molecules in the myocardium) and in the periphery (circulating anti-heart autoantibodies, raised cytokine levels). Viral infections or other environmental noxae may act as a second hit or as precipitating/accelerating factors. The finding that anti-heart autoantibodies precede several years and predict the subsequent development of DCM or left ventricular dysfunction in relatives of patients with DCM from both familial and nonfamilial pedigrees is in keeping with this model [135] and mirrors what happens in other extra-cardiac autoimmune diseases ([Figure 1]) [10].

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REFERENCES


Major causes of myocarditis

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**Helminthic**

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| Echinococcosis | |
| Filariasis | |
| Paragonimiasis | |
| Schistosomiasis | |
| Strongyloidiasis | |
| Trichinosis | |

**Virus-immune hypothesis in dilated cardiomyopathy**

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Following acute viral myocarditis, subjects who are not genetically predisposed to autoimmunity develop a self-limited disease and recover completely. In contrast, in individuals with a genetic predisposition to autoimmunity, a viral infection may initiate a chronic autoimmune myocarditis leading to dilated cardiomyopathy.

Clinical manifestations and diagnosis of myocarditis in adults

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INTRODUCTION — Myocarditis can be produced by a variety of different causes, many of which are infectious (table 1) [1]. In developed countries, viral infection is the most frequently presumed cause of myocarditis. In the 1980s and 1990s, enteroviruses (coxsackie B and others) were frequently associated with myocarditis and dilated cardiomyopathy. In the past 10 years, however, other viruses, including adenovirus, parvovirus B19, hepatitis C, and herpes virus 6, have emerged as significant pathogens [2]. In many developing countries, rheumatic carditis, Chagas disease, and disorders associated with advanced HIV are important causes of myocarditis.

Although histology remains the gold standard for establishing the diagnosis of myocarditis, low-risk patients are often presumed to have myocarditis on the basis of a compatible clinical scenario, suggesting new onset inflammatory cardiomyopathy and cardiovascular magnetic resonance (CMR) features without an endomyocardial biopsy (EMB). However, clinical features at presentation in myocarditis are polymorphic and there is no sign, symptom, or constellation of clinical features that is diagnostic of acute or subacute/chronic myocarditis.

The clinical manifestations and diagnosis of myocarditis will be reviewed here. The etiology, pathogenesis, treatment, and prognosis of this disorder are discussed separately. (See "Etiology and pathogenesis of myocarditis" and "Treatment and prognosis of myocarditis in adults".)

DEFINITION — Myocarditis is an inflammatory disease of the myocardium. As discussed below, the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) definition specifies diagnosis by established histological (Dallas criteria), immunological, and immunohistochemical criteria [3], though many patients with clinical manifestations of myocarditis do not undergo endomyocardial biopsy so a definitive diagnosis is not established. (See 'Dallas criteria' below and 'WHO/ISFC definition' below and 'Endomyocardial biopsy' below.)

Inflammatory cardiomyopathy is defined as myocarditis accompanied by cardiac dysfunction [3]. Inflammatory cardiomyopathy can lead to dilated cardiomyopathy or other cardiomyopathies. (See "Definition and classification of the cardiomyopathies".)

CLINICAL FEATURES

Clinical manifestations

Variable presentation — The clinical manifestations of myocarditis are highly variable ranging from subclinical disease to fatigue, chest pain, heart failure, cardiogenic shock, arrhythmias, and sudden death (table 2) [4-7]. There is no population-based epidemiologic study that has defined presenting symptoms of acute or subacute/chronic myocarditis; this is due in part to the absence of a safe and sensitive noninvasive diagnostic test that can confirm the diagnosis.

The variability in presentation reflects the variability in histological disease severity, etiology, and disease stage at presentation. Myocardial inflammation may be focal or diffuse, involving any or all cardiac chambers. Severe, diffuse myocarditis can result in acute dilated cardiomyopathy. The histological features of chronic myocarditis are usually more subtle, and include altered n leukocyte antigen (HLA) and adhesion molecule expression, and inflammatory cell infiltrates that are apparent only on cell specific immunostains (ie, CD3 for T lymphocytes and CD68 for macrophages) [8].

Early studies suggested that cardiac involvement may have occurred in 3.5 to 5 percent of patients during outbreaks of coxsackievirus infection [9,10]. However, there is significant difficulty in establishing a diagnosis of myocarditis because endomyocardial biopsy (EMB) is not performed in many suspected cases and there is no noninvasive "gold standard."
The sensitivity of EMB using conventional histology (Dallas criteria) for myocarditis may be as low as 10 to 35 percent due to variability in interpretation and sampling error, but application of immunohistochemistry and viral polymerase chain reaction (PCR) have yielded higher sensitivity [11-16]. (See 'Endomyocardial biopsy' below and "Etiology and pathogenesis of myocarditis").

Many cases of myocarditis likely go undetected because they are subclinical or present with nonspecific signs. For example, the rate of troponin rise after smallpox vaccination is 1:200, yet the rate of clinically suspected myocarditis has been reported to be approximately 1:5500 [17]. Subtle cardiac symptoms and signs may be overshadowed by systemic manifestations of the underlying infection or disease process. In the early stages of viral myocarditis, for example, the patient may have fever, myalgias, and muscle tenderness. The muscle symptoms are attributable to myositis induced by a myotropic virus such as coxsackievirus A. In the United States Myocarditis Treatment Trial, 89 percent of subjects reported a syndrome consistent with a viral prodrome [18].

**Heart failure** — Many symptomatic cases of postviral or lymphocytic myocarditis present with a syndrome of heart failure and dilated cardiomyopathy. In a large review of 1230 cases of initially unexplained cardiomyopathy in the United States, 9 percent were thought to be due to myocarditis [19]. A similar prevalence (10 percent) was noted in the Myocarditis Treatment Trial in which EMB was performed in over 2200 patients with unexplained heart failure of less than two years duration [18].

In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, rapidly evolving diffuse, severe myocarditis can result in acute myocardial failure and cardiogenic shock. Signs of right ventricular failure include increased jugular venous pressure, hepatomegaly, and peripheral edema. Patients with predominant left ventricular involvement, present with symptoms of pulmonary congestion including dyspnea, orthopnea, pulmonary rales, and, in severe cases, acute pulmonary edema. (See "Evaluation of acute decompensated heart failure".)

**Chest pain** — Chest pain may reflect associated pericarditis. (See "Myopericarditis".) Myocarditis can mimic myocardial ischemia and/or infarction both symptomatically and on the electrocardiogram, particularly in younger patients [12,20-23]. As an example, in one study of 45 patients presenting with suspected acute coronary syndrome with a normal coronary angiogram, 35 (78 percent) had a diffuse or focal myocarditis on myocardial imaging [21]. Complete recovery of left ventricular function occurred at six months in 81 percent of these patients. Focal wall motion abnormalities associated with myocarditis may be due to localized inflammation or ischemia caused by coronary spasm [24]. (See Differential diagnosis below.)

**Sudden cardiac death** — Myocarditis may present with unexpected sudden death, presumably due to ventricular tachycardia or fibrillation [25-28]. In an autopsy series of patients under age 40 who presented with sudden death in the absence of known heart disease, myocarditis was responsible for 22 percent of cases under age 30 and 11 percent in older subjects [26]. In another autopsy study of sudden death occurring in competitive athletes, myocarditis was present in 6 percent of cardiovascular deaths [29]. In a series of autopsies in military recruits, myocarditis accounted for 20 percent of deaths due to identifiable structural cardiac abnormalities [28]. (See "Pathophysiology and etiology of sudden cardiac arrest".)

**Arrhythmias** — A number of arrhythmias may be seen in patients with myocarditis. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias, while palpitations secondary to premature atrial or, more often, ventricular extrasystoles are common. Bradycardia and syncope due to new-onset unexplained heart block may also occur both in infectious (eg, Lyme disease) and in immune-mediated forms of myocarditis (eg, sarcoidosis, giant cell myocarditis). (See "Clinical manifestations of Lyme disease in adults", section on 'Carditis' and "Cardiac sarcoidosis".)

**Physical examination** — In addition to signs of fluid overload, the physical examination often reveals direct evidence of cardiac dysfunction in symptomatic patients. (See "Evaluation of the patient with suspected heart failure", section on 'Physical examination'.)

- S3 and occasionally S4 gallops are important signs of impaired ventricular function, particularly when biventricular acute myocardial involvement results in systemic and pulmonary congestion. (See "Auscultation of heart sounds".)
- If the right or left ventricular dilatation is severe, auscultation may reveal murmurs of functional mitral or tricuspid insufficiency. (See "Auscultation of cardiac murmurs".)
- A pericardial friction rub and/or effusion may be detected in some patients with myocarditis and associated pericarditis (myopericarditis). (See "Myopericarditis".)
Initial testing — Initial testing generally includes electrocardiography, cardiac biomarkers, and generally chest radiography. Routine laboratory studies of blood and urine are often normal or reveal only nonspecific abnormalities. Measurement of brain natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) is recommended if heart failure is suspected but the diagnosis is uncertain.

Electrocardiogram — The electrocardiogram in patients with myocarditis may be normal or show nonspecific abnormalities. Findings may include nonspecific ST changes, single atrial or ventricular ectopic beats, complex ventricular arrhythmias (couplets or nonsustained ventricular tachycardia), or, rarely, atrial tachycardia or atrial fibrillation. High grade heart block is uncommon in lymphocytic myocarditis, but common in Lyme disease, cardiac sarcoidosis, and idiopathic giant cell myocarditis. (See "Lyme carditis", section on 'Atrioventricular conduction abnormalities' and "Cardiac sarcoidosis", section on 'Heart block and arrhythmias' and "Treatment and prognosis of myocarditis in adults" and "Treatment and prognosis of myocarditis in adults", section on 'Giant cell myocarditis'.)

The echocardiogram (ECC) in some patients with myocarditis is similar to the ECG pattern of acute isolated pericarditis (which is suggestive of myopericarditis) or acute myocardial infarction (MI) [12,20-33-30]. Like acute MI, myocarditis may be associated with regional ST elevations and Q waves. Myocarditis should be suspected in young patients who present with a possible MI but have a normal coronary angiogram. In one study of 45 such patients, 35 (78 percent) had a diffuse or focal myocarditis on myocardial imaging [21]. Complete recovery of left ventricular function occurred at six months in 81 percent. (See "Myopericarditis", section on 'Electrocardiogram findings' and "Electrocardiogram in the diagnosis of myocardial ischemia and infarction").

The presence of Q waves or left bundle branch block was associated with higher rates of death or transplantation in some [31] but not in all studies [32,33].

Cardiac biomarkers — Cardiac biomarker elevations reflecting myocardial necrosis are seen in some but not all patients with myocarditis. Experimental and clinical findings suggest that elevations of cardiac troponin I or T (cTnI or cTnT) levels are more common than creatine kinase MB (CK-MB) elevations in patients with biopsy-proven myocarditis (34 versus 6 percent and 53 versus 2 percent in two reports) [34,35]. The elevations of cTnI were correlated with a short duration (less than one month) of heart failure symptoms [34], suggesting that the majority of myocardial necrosis occurs early in the course of the disease. Persistent elevations in cardiac enzymes are indicative of ongoing necrosis. (See "Troponins and creatine kinase as biomarkers of cardiac injury").

Chest radiograph — The heart size on chest radiograph varies from normal to enlarged with or without pulmonary vascular congestion and pleural effusions (image 1). In some cases, biventricular cardiomegaly is associated with the absence of pulmonary congestion such as in those with right ventricular failure and/or moderate or severe tricuspid regurgitation. However, chest radiography has limited sensitivity for identification of cardiomegaly or for diagnosis of heart failure. (See "Evaluation of the patient with suspected heart failure", section on 'Chest radiograph'.)

BNP or NT-proBNP — BNP or NT-proBNP level should be measured if heart failure is suspected but the diagnosis is uncertain; these are the most sensitive initial tests for heart failure. (See "Evaluation of the patient with suspected heart failure", section on 'Initial testing' and "Natriuretic peptide measurement in heart failure").

Cardiac imaging

Echocardiography — The echocardiogram is the key method of detecting impaired ventricular function in suspected myocarditis, even when subclinical [36,37]. Findings include left ventricular dilation, changes in left ventricular geometry (eg, development of a more spheroid shape), and wall motion abnormalities. The systolic dysfunction is generally global, but may be regional or segmental. An abnormal tissue Doppler signal may provide additional evidence of myocarditis although data are limited [38].

Mild impairment in myocardial contractility may be evident only when the study is performed at rest rather than during exercise. However, exercise-induced wall motion abnormalities may also be seen; they are usually due to microvascular dysfunction.

The echocardiogram can also detect coexistent pericardial involvement, silent intracardiac thrombi (movie 1), and functional mitral or tricuspid regurgitation.

Fulminant and acute myocarditis are both associated with left ventricular dilatation and systolic dysfunction. The extent of left ventricular dysfunction and dilatation does not necessarily distinguish the two. Patients with fulminant myocarditis typically have near normal left ventricular diastolic dimensions and mildly increased septal thickness, while those with...
acute myocarditis have normal or increased left ventricular diastolic dimensions and normal or increased septal thickness [39]. Patients with fulminant myocarditis who survive the acute illness frequently have dramatic improvement in systolic function within several months, while recovery of systolic function is less common in patients with acute myocarditis [32,39]. A spherical-shaped ventricle commonly seen in acute myocarditis tends to remodel to a more normal elliptical shape over a several month period [40]. (See ‘Clinicopathologic classification’ below.)

Three-dimensional echocardiography may provide more accurate and objective noninvasive ejection fraction measurement than standard two-dimensional echocardiography but requires adequate acoustic windows.

**Radionuclide ventriculography** — Since ventricular function is generally assessed by echocardiography, radionuclide ventriculography is usually not needed. However, radionuclide studies can be useful when transthoracic echocardiographic images are suboptimal and transesophageal echocardiography or cardiovascular magnetic resonance (CMR) is unavailable. There may be less variability in the ejection fraction measurement obtained with serial radionuclide ventriculography as compared to measurement by two-dimensional echocardiography because its analysis is less operator-dependent. (See "Noninvasive methods for measurement of left ventricular systolic function").

**Cardiovascular magnetic resonance** — CMR imaging enables detection of various features of myocarditis, including inflammatory hyperemia and edema, myocyte necrosis and scar, changes in ventricular size and geometry, regional and global wall motion abnormalities, and identification of accompanying pericardial effusion [41,42]. CMR findings can help confirm the diagnosis of myocarditis though sensitivity is variable and time-dependent and abnormalities are non-specific. (See “Clinical utility of cardiovascular magnetic resonance imaging” and “Clinical utility of cardiovascular magnetic resonance imaging”, section on ‘Acute myocarditis’.)

Findings on CMR include increases in T1 and T2 signal intensity consistent with edema, increase early myocardial contrast enhancement relative to skeletal muscle consistent with hyperemia, and presence of late gadolinium enhancement (LGE) consistent with necrosis or scar (image 2) [41-43]. LGE appears to be less sensitive than global relative enhancement (gRE) or edema ratio for detection of clinically suspected acute myocarditis [13,44], so lack of LGE does not exclude acute myocarditis. The best diagnostic performance may be obtained by requiring positivity of any two of these three sequences. This criterion yielded a sensitivity of 76 percent and specificity of 96 percent in 25 patients with clinically suspected acute myocarditis with pseudo-ischemic presentation [44].

An expert consensus paper acknowledged that EMB with histopathology (Dallas criteria), immunohistochemistry, and molecular PCR tools are the accepted standards for diagnosis of myocarditis and limited data are available on the diagnostic accuracy of CMR relative to this standard [41].

The potential utility of combined CMR and EMB was investigated by a study of 82 patients admitted with troponin-positive chest pain who had no significant coronary artery disease on angiography [45]. Myocarditis was the most frequent diagnosis by both CMR and EMB and was detected with a higher frequency by EMB (58 versus 81 percent). Myocarditis was diagnosed most frequently (78 of 82 patients or 95 percent) when either CMR or EMB criteria were accepted as diagnostic. The findings suggest that combined application of CMR and EMB may provide diagnostic synergy and overcome some of the individual limitations of CMR and EMB. However, the specificity of this approach is uncertain.

CMR studies have suggested that myocarditis often begins as a focal process [2,14,46]:

- In a report of 32 patients with clinically suspected myocarditis, 28 (88 percent) had one or more foci of LGE, most often in the left ventricular free wall [14]. Active myocarditis was found in 19 of 21 patients in whom EMB was performed in the LGE region and in only 1 of 11 patients in whom the biopsy was performed outside the LGE region. Thus, use of CMR data to guide endomyocardial biopsy may increase the diagnostic yield. (See ‘Dallas criteria’ below.)
- In a German study, different viral pathogens were associated with different LGE focal patterns [2]. Patients with parvovirus B19 (PVB19) have left ventricular lateral wall subepicardial LGE, while patients with human herpes simplex virus 6 (HHV6) and especially HHV6/PVB19 have septal LGE and heart failure. However, in a later study, CMR findings failed to be associated with viral genome PCR positivity or specific virus type [13].

The pattern of LGE in myocarditis can generally be distinguished from that in ischemic cardiomyopathy. In myocarditis, LGE preferentially involves the epicardium and mid myocardium with sparing of the endocardium [47]. In ischemic cardiomyopathy, LGE reflects the distribution of MI, which typically involves the endocardium with variable extension into the mid myocardium and epicardium.
Late gadolinium enhancement has also been described in some patients with nonischemic cardiomyopathy where the etiology is less clear [48]. Some patients with new onset nonischemic cardiomyopathy who have myocardial enhancement on CMR may have myocarditis, although this has not been established. (See "Clinical utility of cardiovascular magnetic resonance imaging").

**Cardiac catheterization** — In selected patients with myocarditis, cardiac catheterization may be helpful in characterizing and managing their hemodynamic status. (See "Pulmonary artery catheterization: Indications, contraindications, and complications in adults", section on 'Indications'.)

Although generally not required, coronary angiography is indicated in selected patients with clinical presentation indistinguishable from an acute coronary syndrome, symptom-limiting coronary disease, or high-risk features for ischemic heart disease on noninvasive testing. (See "Overview of the acute management of ST elevation myocardial infarction" and "Coronary angiography and revascularization for unstable angina or non-ST elevation acute myocardial infarction" and "Stable ischemic heart disease: Overview of care", section on 'Coronary angiography and revascularization'.)

**Other tests** — Gallium scanning may be of value in some cases, showing evidence of severe myocardial cellular infiltration [49]. However, it has largely been replaced by CMR. (See 'Cardiovascular magnetic resonance' above.)

Positron emission tomography using fluorine-18 labeled deoxyglucose (FDG-PET) imaging of viral myocarditis has been reported but data are limited [50].

**DIAGNOSIS** — There are two clinical issues relevant to the diagnosis of myocarditis: when it should be suspected and how the diagnosis is confirmed.

**When to suspect myocarditis** — The clinical presentation of myocarditis is highly variable and myocarditis can mimic other noninflammatory cardiac disorders. Therefore, a high level of clinical suspicion is needed. Myocarditis should be suspected in patients with or without cardiac signs and symptoms (table 2), who have a rise in cardiac biomarkers (eg, troponin), electrocardiographic changes suggestive of acute myocardial injury, arrhythmia, or abnormalities of cardiac function (typically on echocardiogram or cardiac magnetic resonance [CMR]), particularly if the clinical findings are new and unexplained.

Acute myocarditis should be suspected in the following clinical settings:

- Onset of otherwise unexplained cardiac abnormalities such as heart failure, cardiogenic shock, or arrhythmias.
  - Age at onset varies but is typically between 20 to 50 years [51].
  - Some patients have history of a viral illness or have rash and eosinophilia following a new drug or vaccine, but many do not. As an example, a history of recent upper respiratory infection or enteritis was present in 36 percent of patients in a series of patients with biopsy-proven myocarditis [32].
- Acute or subacute development of left ventricular (LV) systolic dysfunction (global or regional) without apparent etiology [52].
  - Some patients have evidence of systemic viral, bacterial, rickettsial, fungal, or parasitic infection but many do not. Since many cardiotropic viruses, including coxsackie A, are also myotropic, the concurrent presence of muscle aching and particularly muscle tenderness in this setting may increase suspicion of myocarditis.
  - One presentation is an acute viral infection (eg, exanthematous disease in children and adults due to parvovirus B19) accompanied by tachycardia out of proportion to fever. (See "Clinical manifestations and diagnosis of human parvovirus B19 infection").
- Pericarditis (infectious or idiopathic) with accompanying cardiac biomarker elevation suggestive of myopericarditis. (See "Clinical presentation and diagnostic evaluation of acute pericarditis", section on 'Clinical features' and "Myopericarditis'.)
- When a patient (particularly one without cardiovascular risk factors) presents with clinical signs and symptoms of an acute myocardial infarction, particularly if the coronary angiogram is normal [12,20-23,52].

Thus, a combination of clinical presentation and noninvasive diagnostic findings including typical CMR abnormalities suggest the diagnosis of myocarditis. A definitive diagnosis of myocarditis is based upon endomyocardial biopsy (EMB), including histology (Dallas criteria) as well as immunohistochemical stains and detection of viral genomes by molecular techniques, mainly polymerase chain reaction (PCR). This approach is supported by the World Health Organization (WHO) classification and definition of cardiomyopathies as well as later expert scientific statements [1,3,53,54], though many patients with suspected myocarditis are not considered candidates for EMB. Analysis of the EMB is also helpful in
identifying the etiopathogenetic form of myocarditis, eg, giant cell myocarditis, sarcoidosis, and other autoimmune forms as well as infectious causes \[3,53,54\].

In patients with clinically suspected myocarditis, the decision of whether to proceed with EMB should be based upon the likelihood that EMB will significantly impact patient management \[55\]. (See *When should endomyocardial biopsy be performed?* below.)

**Differential diagnosis** — When the patient presents with heart failure and a cardiomyopathy presumed to be due to myocarditis, the differential diagnosis includes ischemic heart disease, valvular heart disease, other causes of cardiomyopathy, congenital heart disease, and pulmonary disease. Echocardiography is helpful for distinguishing many of these disorders. (See "Determining the etiology and severity of heart failure or cardiomyopathy".)

Myocarditis may present similarly to ischemic heart disease with chest pain, electrocardiographic abnormalities, and elevated cardiac biomarkers. Wall motion abnormalities seen in myocarditis range from regional wall motion abnormalities (which may be in noncoronary or coronary distributions) to global abnormalities. Exercise-induced wall motion abnormalities may be identified in patients with ischemic heart disease or myocarditis. In patients with myocarditis, these wall motion abnormalities have been attributed to microvascular dysfunction. Coronary angiography is indicated in selected patients with clinical findings suggestive of coronary disease. Coronary spasm, occasionally severe, may accompany myocarditis and cause angina. (See *Cardiac catheterization* above.)

Myocarditis may also mimic arrhythmogenic right ventricular cardiomyopathy \[56,57\]. Patients with either condition may present with left bundle branch block morphology ventricular tachycardia and right ventricular echocardiographic and CMR abnormalities including late gadolinium enhancement. Since some patients with myocarditis fulfill clinical criteria for arrhythmogenic right ventricular cardiomyopathy, a high index of suspicion is required. EMB is helpful in distinguishing these two disorders. (See "Clinical manifestations and diagnosis of arrhythmogenic right ventricular cardiomyopathy".)

Other laboratory testing such as serum protein electrophoresis, fat aspirate and CMR for amyloidosis, and ferritin levels and CMR for myocardial iron overload are helpful in excluding other causes of ventricular dysfunction. (See "Clinical manifestations and diagnosis of amyloid cardiomyopathy" and "Approach to the patient with suspected iron overload", section on "Tests available for documenting iron overload".)

Of note, biopsy-proven myocarditis may occur in association with other causes of cardiomyopathy, including cardiac amyloidosis \[58\] and hypertrophic cardiomyopathy \[59\] and may affect prognosis of these disorders. (See *Natural history of hypertrophic cardiomyopathy*.)

**Endomyocardial biopsy**

*When should endomyocardial biopsy be performed?* — Once other causes of heart failure (such as ischemic heart disease, critical valvular lesions, and restrictive and hypertrophic cardiomyopathies) have been excluded, the need for an EMB should be based upon the likelihood that the results will change management \[55\]. This will depend upon the time course, severity, and characteristics of the presentation as addressed in the 2007 American Heart Association/American College of Cardiology Foundation/European Society of Cardiology (AHA/ACCF/ESC) scientific statement on EMB (table 3) \[60\]. EMB is recommended for patients with fulminant heart failure (new onset heart failure of less than two weeks duration associated with hemodynamic compromise) or new onset heart failure of two to three months duration associated with a dilated left ventricle and new ventricular arrhythmias, second or third degree AV block, or failure to respond to usual care within one to two weeks. EMB was suggested in selected cases in patients with advanced atrioventricular (AV) block, ventricular arrhythmias, or refractory heart failure and dilated cardiomyopathy associated with eosinophilia. EMB may also be considered in several other scenarios when other evaluation is inconclusive and a diagnosis of myocarditis may impact treatment or prognosis. The 2013 ESC position statement on myocarditis suggested additional potential criteria for EMB as discussed separately \[1\]. (See *Endomyocardial biopsy*.)

**Histology** — Histologic examination of EMB in myocarditis reveals cellular infiltrates, which are usually histiocytic and mononuclear with or without associated myocyte damage. Specific histological forms of myocarditis include eosinophilic, granulomatous, and giant cell myocarditis. The infiltrates are of varying severity and are often associated with myocyte necrosis and disorganization of the myocardial cytoskeleton (picture 1A-B). With subacute and chronic myocarditis, interstitial fibrosis may replace myocytes, and myofiber hypertrophy may also be seen (picture 2). Criteria for the histological diagnosis of myocarditis include the Dallas criteria that rely on standard histological stains, and several others that use immunohistological criteria.
Histopathologic diagnosis of a specific cause of myocarditis is occasionally possible in patients with toxoplasmosis, Chagas disease, Lyme carditis, cytomegalovirus myocarditis, and trichinellosis. Electron microscopic examination is occasionally useful to exclude anthracycline toxicity, but other forms of anthracycline-related myocardial dysfunction have entirely non-specific findings in the myocardium. (See "Endomyocardial biopsy", section on ‘Indications’.)

**Dallas criteria** — The Dallas criteria were developed by a panel of cardiac pathologists as a working standard for the United States Myocarditis Treatment Trial; these criteria are now used by most investigators to define the disease [61]:

- Active myocarditis is defined as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease." The infiltrates are usually mononuclear, but may be neutrophilic or, occasionally, eosinophilic (picture 1A–B).
- “Borderline myocarditis” is the term used when the inflammatory infiltrate is too sparse or myocyte injury is not demonstrated.

There are, however, concerns about the diagnostic accuracy of the Dallas criteria for the diagnosis of myocarditis [11,62,63]. In one report of 38 cases, using autopsy as the gold standard, the sensitivity and specificity of EMB were approximately 60 and 80 percent, respectively [63]. A lower sensitivity of 35 percent has been noted when a clinical and functional gold standard is used [62].

The low sensitivity of the Dallas criteria is likely in part due to the focal and transient nature of the inflammatory infiltrates [14,63]. In the above autopsy study of 38 cases, right ventricular biopsy was positive in 63 percent of patients, left ventricular biopsy was positive in 55 percent of patients but only 17 to 20 percent of individual biopsy specimens were positive [63]. In a report comparing CMR and histology, the most common site of focal involvement was the epicardial surface of the left ventricular free wall, while most EMBs are obtained from the right ventricular side of the interventricular septum [14]. Active myocarditis was found in 19 of 21 patients with EMB directed by CMR imaging and was infrequent in regions not identified by CMR imaging. However, the clinical applicability of this method is uncertain given the risk of left ventricular free wall biopsy.

Another problem with the Dallas criteria is that even expert pathologists often disagree on the interpretation of myocardial biopsy material [11]. For example, in the Myocarditis Treatment Trial, the diagnosis was confirmed by the expert panel in only 64 percent of cases [18].

An additional limitation of the Dallas criteria is that viral genome may be present in the myocardium without sufficient histologic changes to meet the Dallas criteria, as discussed below. (See ‘PCR and immunohistochemistry’ below.)

**WHO/ISFC definition** — The WHO/International Society and Federation of Cardiology (ISFC) definition of myocarditis includes histological (Dallas) criteria as well as immunological and immunohistochemical criteria [3]. This approach was endorsed in subsequent scientific statements [1,53,54].

The ESC position statement defined “immunohistochemical criteria” to include an abnormal inflammatory infiltrate defined as ≥14 leukocytes/mm² including up to 4monocytes/mm² with the presence of CD3-positive T-lymphocytes ≥7 cells/mm² [1].

**PCR and immunohistochemistry** — Detection of viral genome by PCR may be used to identify specific viral pathogens, although the clinical value of viral genome detection remains uncertain, especially in the absence of histologic criteria for myocarditis.

Case series from the 1990s suggested that enteroviral genomes in the myocardium of heart failure patients were a biomarker of worse outcomes. An observational study evaluated 41 patients with progressive heart failure for six months unresponsive to standard therapy who were found to have active lymphocytic myocarditis on biopsy [64]. All 41 were treated with prednisone and azathioprine for six months, and 21 had an improvement in ejection fraction at the end of treatment. Of the 20 patients who did not respond to immunosuppressive therapy, 17 had viral genomes (including six with enterovirus) detected by PCR. Of the 21 patients who did respond to treatment, only three had a positive PCR assay (all for hepatitis C virus).

These findings are consistent with those in another study in which persistence of viral genome by PCR was associated with progressive left ventricular dysfunction, while clearance of viral genome was associated with improved left ventricular function [65]. (See “Treatment and prognosis of myocarditis in adults”.)
However, viral genome is often present in myocardium without sufficient histologic changes to meet the Dallas criteria [11,15,66]. As an example, viral pathogens, including HHV6 and parvovirus B19, were detected in 67 percent of 245 adults with dilated cardiomyopathy with no accompanying cellular immune response [67].

A case series of 181 adults with clinically suspected viral myocarditis found that neither detection of viral genomes nor Dallas criteria were predictive of time to death or heart transplantation [15]. Outcomes were predicted by immunohistologic evidence of inflammatory infiltrates, and advanced New York Heart Association functional class at entry and inversely related to provision of beta blocker therapy. One interpretation of these data is that certain viruses are pathogenic in acute and chronic dilated cardiomyopathy, but some viral infections may be unrelated to the pathogenesis of cardiomyopathy, especially in the absence of the Dallas histologic criteria for myocarditis. (See 'Identifying the cause of myocarditis' below.)

**Identifying the cause of myocarditis** — Causes of myocarditis include infectious agents, cardiotoxins, hypersensitivity reactions, systemic disorders, and radiation (table 1). However, an etiology is often difficult to identify and the cause is frequently unknown.

The history, symptoms, and extracardiac signs may suggest specific etiologies of myocarditis such as infectious processes (eg, toxoplasmosis, Chagas disease, Lyme disease, trichinellosis), toxins, or autoimmune diseases. For example, a viral prodrome of fever, myalgias, and muscle tenderness may precede viral myocarditis, while a delayed hypersensitivity reaction may be first apparent from a cutaneous rash, eosinophilia, and elevated liver enzyme levels. (See "Toxoplasmosis in immunocompetent hosts", section on 'Diagnosis' and "Chagas heart disease: Clinical manifestations and diagnosis" and "Lyme carditis", section on 'Diagnosis' and "Trichinellosis", section on 'Diagnosis'.)

A history of smallpox vaccination within the 30 days prior to symptom onset should prompt consideration of the diagnosis of hypersensitivity myocarditis or myopericarditis. Because tests for vaccinia viremia are only rarely positive and viral antibody titers rise after successful vaccination, these tests are not helpful, and the clinical suspicion is based primarily upon the temporal relationship [68]. (See "Etiology and pathogenesis of myocarditis", section on 'Pathogen' and "Myopericarditis", section on 'Vaccinia-associated myopericarditis'.)

As described above, detection of viral genome on EMB specimen may suggest a cause, particularly in the presence of histologic evidence of myocarditis. (See 'PCR and immunohistochemistry' above.)

Measurement of acute and convalescent antibody titers appears to be of little use in determining the etiology in patients with dilated cardiomyopathy, since there was no difference between the patients and matched community controls who shared the same environment or household contacts [69]. Similarly, viral culture of myocardial samples for viruses is rarely successful.

Preliminary studies suggest a potential future role for measurement of serum anti-heart autoantibodies. Anti-heart autoantibodies to various autoantigens are found in patients with myocarditis or dilated cardiomyopathy (DCM) [32]. (See "Etiology and pathogenesis of myocarditis", section on 'Autoimmune mechanisms'.) Lack of viral genome on EMB with detectable serum anti-heart autoantibodies suggests immune-mediated DCM or myocarditis and may predict beneficial response to immunosuppression [64]. Among asymptomatic relatives of DCM patients, the presence of anti-heart autoantibodies is an independent predictor for development of DCM [70].

**CLINICOPATHOLOGIC CLASSIFICATION** — A clinicopathologic classification utilizing both histologic and clinical features may provide prognostic information about patients with heart failure due to myocarditis. One group proposed the following classification, though not all experts agree with such distinct clinicopathologic forms (see 'Histology' above) [71]:

- **Fulminant myocarditis** — Fulminant myocarditis was defined as presenting with acute heart failure up to two weeks after a distinct viral prodrome. Patients have severe cardiovascular compromise and may require mechanical circulatory support. Multiple foci of active lymphocytic myocarditis are common, and ventricular systolic dysfunction often normalized in patients surviving the acute illness [72].
- **Acute myocarditis** — Acute myocarditis was defined as presenting with a less distinct onset of illness, established ventricular systolic dysfunction, and possible progression to dilated cardiomyopathy.
- **Chronic active myocarditis** — Chronic active myocarditis was also described as presenting with a less distinct onset of illness, with frequent clinical and histologic relapses, development of ventricular systolic dysfunction associated with chronic inflammatory changes, and mild to moderate fibrosis on endomyocardial biopsy.
Chronic persistent myocarditis — Chronic persistent myocarditis, which was also described as presenting with a less distinct onset of illness, was characterized by a persistent histologic infiltrate, often with foci of myocyte necrosis, and no ventricular systolic dysfunction despite persistent chest pain or palpitation.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

Basics topics (see "Patient information: Myocarditis (The Basics)")

SUMMARY AND RECOMMENDATIONS

Myocarditis should be suspected in patients with or without cardiac signs and symptoms (table 2) who present with a rise in cardiac biomarker levels, change in electrocardiogram suggestive of acute myocardial injury, arrhythmia, or abnormalities of ventricular systolic function, particularly if the these clinical findings are new and unexplained. (See 'When to suspect myocarditis' above.)

The diagnostic evaluation of patients with suspected myocarditis should include the following components:

- History and physical examination should evaluate symptoms and signs of myocarditis (table 2) and address possible causes of the myocarditis or cardiomyopathy.
- Initial laboratory testing includes an electrocardiogram (ECG), biomarkers, and generally a chest radiograph. Natriuretic peptide measurement is indicated if the diagnosis of heart failure is uncertain. (See 'Initial testing' above.)
- An echocardiogram is performed to evaluate regional and global ventricular function, valvular function, and other potential causes of cardiac dysfunction. Cardiovascular magnetic resonance (CMR) imaging may provide supportive evidence of myocarditis. (See 'Cardiac imaging' above.)
- In selected patients with suspected myocarditis, cardiac catheterization may aid determination of hemodynamic status. Coronary angiography is indicated in selected patients with clinical findings suggestive of acute coronary syndrome. (See 'Cardiac catheterization' above.)
- Potential indications for endomyocardial biopsy (EMB) and other testing are reviewed.

A decision on whether to perform EMB is made following consideration of the clinical presentation and test results.

- After exclusion of other causes of heart failure (eg, ischemic heart disease, valvular disease, and restrictive and hypertrophic cardiomyopathies), the need for an EMB will depend upon the time course and severity of the presentation, which suggest the likelihood that EMB results will affect management. (See "Endomyocardial biopsy".)
- Additional information obtained by other laboratory testing (including appropriate serum tests for autoimmune disease, serum protein electrophoresis and fat aspirates for amyloidosis, and ferritin levels for hemochromatosis) also guide the decision to proceed to EMB.
- Most patients presenting with subacute to chronic heart failure in whom a diagnosis of idiopathic dilated cardiomyopathy is made should first be managed with appropriate therapy for heart failure. (See "Overview of the therapy of heart failure due to systolic dysfunction".) Most of these patients will respond to medical therapy alone and do not require EMB.
- Indications for EMB include unexplained new-onset heart failure of less than two weeks duration associated with hemodynamic compromise or unexplained new onset heart failure of two weeks to three months duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second-degree atrioventricular (AV) block, third-degree AV block, or refractory heart failure (table 3). Other patient groups who may benefit from EMB are discussed separately. (See "Endomyocardial biopsy", section on 'Indications'.)

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### Clinical features of myocarditis

<table>
<thead>
<tr>
<th>Feature</th>
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</thead>
<tbody>
<tr>
<td>Excessive fatigue or exercise intolerance</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Unexplained sinus tachycardia</td>
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<tr>
<td>S3, S4, or summation gallop</td>
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<tr>
<td>Abnormal electrocardiogram</td>
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<tr>
<td>Abnormal echocardiogram</td>
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<tr>
<td>New cardiomegaly on chest radiograph</td>
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<tr>
<td>Atrial or ventricular arrhythmia</td>
</tr>
<tr>
<td>Partial or complete heart block, new-onset bundle branch block</td>
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<tr>
<td>New onset or worsening heart failure</td>
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<tr>
<td>Acute pericarditis</td>
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<td>Cardiogenic shock</td>
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<td>Sudden cardiac death</td>
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<tr>
<td>Respiratory distress/tachypnea</td>
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<tr>
<td>Hepatomegaly</td>
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</tbody>
</table>

### Sequential chest radiographs in myocarditis

Posteroanterior view sequential chest radiographs in a young man with acute myocarditis (left) and three months later (right). Acutely, cardiomegaly and pulmonary congestion are apparent. Three months later, the lungs have cleared but the patient has developed dilated cardiomyopathy with persistent cardiomegaly.
Cardiovascular magnetic resonance images of a 58-year-old woman with coxsackievirus-induced myocarditis and ventricular tachycardia. Late gadolinium enhancement is seen in a basal to mid anterior and anterolateral distribution (arrows). Note the epicardial to transmural distribution of the enhancement, which is more consistent with myocarditis than myocardial infarction. LV: left ventricle; RV: right ventricle; A: anterior; AL: anterolateral.
# The role of endomyocardial biopsy in fourteen clinical scenarios

<table>
<thead>
<tr>
<th>Scenario number</th>
<th>Clinical scenario</th>
<th>Class of recommendation (I, IIa, IIb, III)</th>
<th>Level of evidence (A,B,C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New onset heart failure of <strong>less than 2 weeks</strong> duration associated with a normal size or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New onset heart failure of <strong>2 weeks to 3 months</strong> duration associated with a dilated left ventricle, and new ventricular arrhythmias, second or third degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of <strong>greater than 3 months</strong> duration associated with a dilated left ventricle and new ventricular arrhythmias, second or third degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>IIa</td>
<td>C</td>
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<tr>
<td>9</td>
<td>New onset heart failure of <strong>2 weeks to 3 months</strong> duration associated with a dilated left ventricle, <strong>without</strong> new ventricular arrhythmias, or second or third degree heart block, and that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>B</td>
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<tr>
<td>10</td>
<td>Heart failure of <strong>greater than 3 months</strong> duration associated with a dilated left ventricle, <strong>without</strong> new ventricular arrhythmias, or second or third degree heart block, and that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained hypertrophic cardiomyopathy</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>Suspected arrhythmogenic right ventricular dysplasia/cardiomyopathy</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>14</td>
<td>Unexplained atrial fibrillation</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>