

STATE-OF-THE-ART PAPER

Update on Myocarditis

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Myocarditis is an inflammatory disease of the heart frequently resulting from viral infections and/or post-viral immune-mediated responses. It is one of the important causes of dilated cardiomyopathy worldwide. The diagnosis is presumed on clinical presentation and noninvasive diagnostic methods such as cardiovascular magnetic resonance imaging. Endomyocardial biopsy remains the gold standard for in vivo diagnosis of myocarditis. The therapeutic and prognostic benefits of endomyocardial biopsy results have recently been demonstrated in several clinical trials. Although remarkable advances in diagnosis, understanding of pathophysiological mechanisms, and treatment of acute myocarditis were gained during the last years, no standard treatment strategies could be defined as yet, apart from standard heart failure therapy and physical rest. In severe cases, mechanical support or heart transplantation may become necessary. There is some evidence that immunosuppressive and immunomodulating therapy are effective for chronic, virus-negative inflammatory cardiomyopathy. Further investigations by controlled, randomized studies are needed to definitively determine their role in the treatment of myocarditis. (J Am Coll Cardiol 2012;59:779–92) © 2012 by the American College of Cardiology Foundation

Myocarditis is an inflammatory disease of the myocardium caused by different infectious and noninfectious triggers (Table 1). In 1995, myocarditis was defined by the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) as an inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria (1). Myocarditis often results from common viral infections and post-viral immune-mediated responses. With the development of new molecular techniques such as polymerase chain reaction (PCR) and in situ hybridization, the spectrum of most frequently detected viruses in endomyocardial biopsies (EMB) shifted from classic enteroviruses and adenovirus to mainly parvovirus B19 (PVB19) and human herpesvirus 6 (2,3). In European studies, mainly PVB19 was detected in patients with biopsy-proven myocarditis (4–6). Whether and why there are geographic differences concerning the distribution of different virus species in myocarditis are currently debated (7). Local and temporal epidemiological

differences of virus infections have to be considered, as well as different diagnostic procedures (8). The discussion, whether PVB19 is an innocent bystander or a pathological agent and whether quantification of virus load is a helpful approach, is ongoing (9).

In patients with human immunodeficiency virus infection, myocarditis was observed in >50% of performed autopsies (10). Furthermore, myocarditis can be triggered by nonviral infections, for example, with *Borrelia burgdorferi* (Lyme disease), *Corynebacterium diphtheriae*, or *Trypanosoma cruzi* (Chagas disease) (11). Numerous medications like antipsychotics (e.g., clozapine [12]), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistics (e.g., mesalamine [13]) can induce hypersensitivity eosinophilic myocarditis, which commonly is reversible after withdrawal of the causative agent. Eosinophilic-lymphocytic myocarditis may also occur after smallpox vaccination (14). Systemic autoimmune diseases such as Churg-Strauss syndrome (15) or hypereosinophilic syndrome (Loeffler's disease) (16) can be associated with eosinophilic myocarditis. In case of cardiac sarcoidosis (17) and giant cell myocarditis (18), which are rare causes of inflammatory myocardial disease, early diagnosis and treatment initiation will significantly improve prognosis.

Myocarditis is regarded as a precursor of dilated cardiomyopathy (DCM), which is currently the most frequent reason for heart transplantation (19). Post-mortem data identify myocarditis in 8.6% to 12% of cases of sudden death in young adults (20). Long-term follow-up studies in patients

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Abbreviations and Acronyms

AV	= atrioventricular
CAR	= coxsackievirus and adenovirus receptor
CMR	= cardiovascular magnetic resonance imaging
DCM	= dilated cardiomyopathy
EMB	= endomyocardial biopsy
HF	= heart failure
HLA	= human leukocyte antigen
ICD	= implantable cardiac defibrillator
IFN	= interferon
IL	= interleukin
LGE	= late gadolinium enhancement
LV	= left ventricular
NSAID	= nonsteroidal anti-inflammatory drug
PCR	= polymerase chain reaction
PVB19	= parvovirus B19

with acute myocarditis have documented the development of DCM in 21% of patients over a mean follow-up period of 3 years (21).

Pathophysiology of Myocarditis

The pathophysiology of myocarditis in humans is not completely understood. Murine models of enteroviral myocarditis suggest that the course of viral myocarditis is characterized by 3 phases (Fig. 1) (22). First, the entry of the virus into the myocytes is mediated through a specific receptor. Coxsackieviruses of group B and some adenoviruses use a common transmembrane receptor (coxsackievirus and adenovirus receptor [CAR]) for internalization of the viral genome into the myocyte (23). Coxsackieviruses utilize the deflecting decay accelerating factor (DAF) and adenoviruses special integrins ($\alpha_{v\beta 3}$ and $\alpha_{v\beta 5}$) as coreceptors. In the absence of CAR expression on cardiac myocytes, viral infection and inflammation does not occur (24). In explanted hearts of patients with DCM, higher CAR expression was demonstrated than in the myocardium of patients with other heart diseases or healthy hearts (25). Whether increased human CAR expression is a predisposing factor for facilitating viral myocarditis has to be shown in future studies.

After viral entry acute injury of the myocytes, induced by virus replication leads to myocyte necrosis, exposure of intracellular antigens (e.g., cardiac myosin), and activation

of the host's immune system, which is characterized by the invasion of natural killer cells and macrophages followed by T lymphocytes (Fig. 2). The acute phase of myocarditis takes only a few days. After the acute phase of virus-induced injury, the second phase is characterized by (auto)immune reactions. This subacute phase, which covers few weeks to several months, is defined by activated virus-specific T lymphocytes, which may target the host's organs by molecular mimicry. Cytokine activation (tumor necrosis factor- α , interleukin [IL]-1 and -6) and antibodies to viral and cardiac proteins may aggravate cardiac damage and cause impairment of the contractile function. In most patients with myocarditis, immune response declines with virus elimination, and left ventricular (LV) function recovers without sequelae. However, in some murine models and probably in patients, (auto)immune processes persist independently of detection of virus genome in the myocardium and lead to the chronic phase, which is characterized by myocardial remodeling and development of DCM (26).

Clinical Presentation and Diagnosis of Myocarditis

The clinical manifestation of myocarditis varies with a broad spectrum of symptoms ranging from asymptomatic courses to presentations with signs of myocardial infarction to devastating illness with cardiogenic shock. Chest pain, cardiac arrhythmias, and acute or chronic heart failure (HF) can occur during the course of the disease (4). Hence, the diagnosis of myocarditis based on the clinical presentation alone is usually not possible.

Biomarkers and virus serology. Biomarkers (such as troponins or creatine kinase) lack specificity, but may help to confirm the diagnosis of myocarditis (27,28). In patients with acute myocarditis, serum concentrations of troponin I and T are elevated more frequently than creatine kinase myocardial band fraction (29), and higher levels of troponin T have been shown to be of prognostic value. Nonspecific

Table 1 Etiology of Myocarditis

Etiology	Subgroups Examples
Infectious	<p>Bacterial: <i>Chlamydia</i>, <i>Corynebacterium diphtheria</i>, <i>Legionella</i>, <i>Mycobacterium tuberculosis</i>, <i>Mycoplasma</i>, <i>Staphylococcus</i>, <i>Streptococcus A</i>, <i>Streptococcus pneumoniae</i></p> <p>Fungal: <i>Actinomyces</i>, <i>Aspergillus</i>, <i>Candida</i>, <i>Cryptococcus</i></p> <p>Helminthic: <i>Echinococcus granulosus</i>, <i>Trichinella spiralis</i></p> <p>Protozoal: <i>Toxoplasma gondii</i>, <i>Trypanosoma cruzi</i></p> <p>Viral: Adenoviruses, Echoviruses, Enteroviruses (e.g., Coxsackieviruses), Herpes Viruses (Human Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus 6), Hepatitis C Virus, Human Immunodeficiency Virus (HIV), Influenza A virus, Parvovirus B19</p> <p>Rickettsial: <i>Coxiella burnetii</i>, <i>Rickettsia typhi</i></p> <p>Spirochetal: <i>Borrelia burgdorferi</i>, <i>Leptospira</i>, <i>Treponema pallidum</i></p>
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn's disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematoses, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitivity reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methylodopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab
Toxic	Ethanol
Others	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

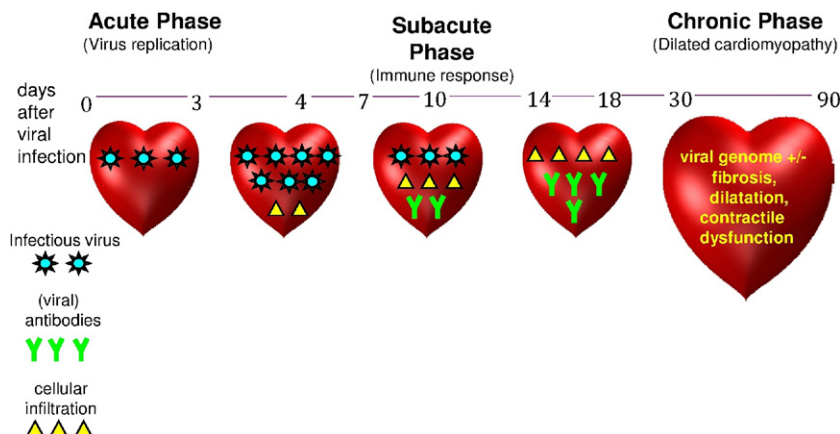


Figure 1 Time Course of Viral Myocarditis

Time course of viral myocarditis in 3 phases (derived from murine models). The acute phase of myocarditis takes only a few days, whereas the subacute and chronic phase covers a few weeks to several months. Modified from Kawai (22).

serum markers of inflammation including leukocytes and C-reactive protein can be elevated in case of acute myocarditis (28,29), but normal values do not exclude an acute myocardial inflammatory process (30).

The utility of virus serology in patients with suspected myocarditis remains unproven. Mahfoud *et al.* (30) investigated the diagnostic value of virus serology in comparison to analyses of EMB including viral genome detection in patients with clinically suspected myocarditis. Only in 5 of 124 patients (4%) there was serological evidence of an infection with the same virus that was detected by nested

PCR in EMB. This result indicates that virus serology should not be commonly used for the diagnosis of myocardial infection in patients with suspected myocarditis. The findings can be explained by the fact that patients are referred for diagnostics and medical treatment with a significant delay from the onset of the initial infection, potentially ranging from some weeks to a few months, when the acute phase of viral myocarditis has already resolved. Moreover, the diagnostic value of serology is also limited in that most viruses involved in the pathogenesis of myocarditis are highly prevalent in the population, for example

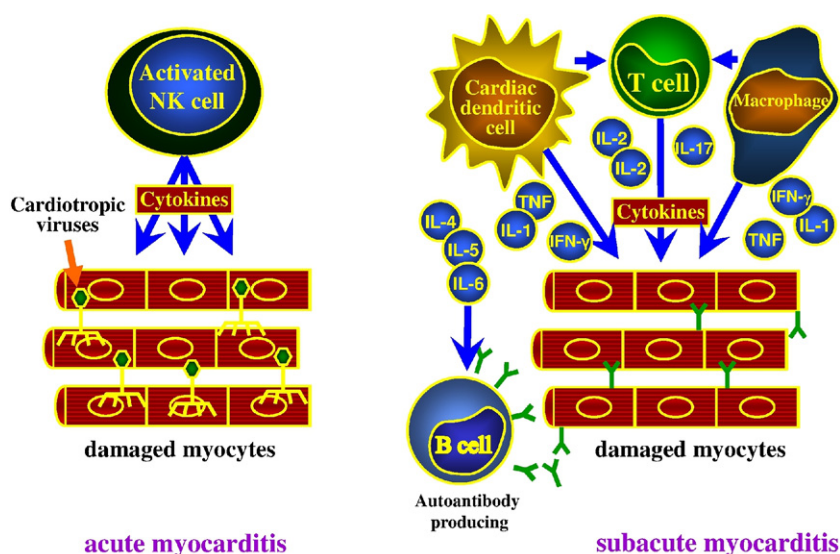


Figure 2 Pathophysiology of Viral Myocarditis

Pathophysiology of viral myocarditis: after viral entry, virus replication leads to acute injury of the myocytes (acute myocarditis) and to activation of the host's immune system (subacute myocarditis). IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

>70% of the population in Germany have been tested seropositive for PVB19 immunoglobulin G antibodies (31). The interpretation of antibody assays is also complicated by other confounders such as reactivation or reinfection (e.g., in case of herpesvirus infections) or by cross reactions, which have been described for infections with Epstein-Barr virus or enterovirus.

Electrocardiogram. The electrocardiogram (ECG) is widely used as a screening tool despite low sensitivity (32). The ECG findings in patients with myocarditis vary from nonspecific T-wave and ST-segment changes to ST-segment elevation mimicking an acute myocardial infarction (27,33). Also, atrial or ventricular conduction delays as well as supraventricular and ventricular arrhythmias can occur in patients with inflammatory heart disease. The presence of Q waves or a new left bundle branch block are associated with higher rates of cardiac death or heart transplantation (34). Recently, the prognostic role of ECG parameters was investigated in patients with suspected myocarditis (35). The ECG recorded at the time of EMB were related to cardiac outcome during long-term follow-up. A QTc prolongation >440 ms, an abnormal QRS axis, and ventricular ectopic beats were associated with poor clinical outcome. A prolonged QRS duration of ≥ 120 ms was found to be an independent predictor for cardiac death or heart transplantation. Hence, the ECG represents an easily available tool for risk stratification in patients with suspected myocarditis.

Echocardiography. There are no specific echocardiographic features of myocarditis. However, echocardiography allows the evaluation of cardiac chamber sizes and wall thickness as well as systolic and diastolic function in patients with myocarditis. It is one of the most important tools to rule out other causes of HF such as valvular heart disease or other cardiomyopathies (hypertrophic or restrictive cardiomyopathy). Especially before an EMB procedure, echocardiography is needed to exclude pericardial effusion and intracavitary thrombi, which have been noted in up to 25% of patients (36). The assessment of different echocardiographic parameters is also of prognostic relevance. Patients with fulminant myocarditis often have normal cardiac chamber sizes with an increased septal thickness secondary to acute myocardial edema, whereas patients with acute myocarditis have marked left ventricular dilation and normal wall thickness (37).

Cardiovascular magnetic resonance. Cardiovascular magnetic resonance (CMR) imaging has evolved as a noninvasive and valuable clinical tool for the diagnosis of myocarditis. In particular, the initial changes in myocardial tissue during the first phase of myocardial inflammation represent attractive targets for a successful CMR-based imaging approach. The T2-weighted edema imaging is routinely used as a tool for evaluating the presence of “acute myocardial inflammation” (Figs. 3A and 3B) (38,39). Moreover, ECG-triggered T1-weighted images are obtained both before and within the first minutes after gadolinium-

diethylenetriaminepentaacetate (Gd-DTPA) infusion. Hence, this sequence has been entitled “myocardial early gadolinium enhancement” (40). Several studies have confirmed the diagnostic value of this sequence, although it is prone to artefacts that decrease specificity (38). Finally, a T1-weighted segmented inversion-recovery gradient-echo sequence (41) was shown to be superior to others used for contrast-enhancement as it improved the difference in signal intensity between myocardial regions with (diseased) and those without (healthy) Gd-DTPA accumulation, thereby leading to a much better contrast. This method is known as “late gadolinium enhancement (LGE) imaging.” In case of myocarditis, LGE imaging revealed 2 common patterns of myocardial damage: either an intramural, rimlike pattern in the septal wall or a subepicardial (patchy) distribution in the free LV lateral wall (Figs. 3C and 3D) (42). However, LGE imaging does not allow to differentiate between acute and chronic inflammation, but represents damaged myocardium. Hence, interpretation of the stage of the illness depends largely on the clinical context. Moreover, the value of LGE imaging for successful diagnosis of myocarditis seems to be related to the histological degree and extent of inflammation (43).

Each individual CMR method has individual advantages but also disadvantages in the diagnosis of myocarditis. Consequently, the combination of these methods is currently regarded as the most appropriate noninvasive approach with the highest sensitivity and specificity (38,40). Because there is a high diagnostic conformity between CMR-based and biopsy-based results, it seems to be reasonable to initially perform CMR in patients with clinically suspected myocarditis and/or nonischemic cardiomyopathy (43). However, if the diagnosis of myocarditis is merely based on the CMR study, then detailed information about the degree of inflammation, the presence of special forms of myocarditis (e.g., giant cell or eosinophilic myocarditis, which require specific therapies), or the presence and type of virus is not available. In addition, less severe forms of myocarditis may not be detected by CMR because of its limited spatial resolution as compared to EMB.

Endomyocardial biopsy. The gold standard in diagnosis of myocarditis is still the EMB. According to the Dallas criteria, acute myocarditis is defined by lymphocytic infiltrates in association with myocyte necrosis (Figs. 4A and 4B). Borderline myocarditis is characterized by inflammatory infiltrates without evidence of myocyte necrosis (44). The Dallas criteria are limited by the high interobserver variability in interpreting biopsy specimens (in particular with regard to borderline myocarditis) and because noncellular inflammatory processes cannot be detected (45). Thus, immunohistochemistry (Figs. 4B and 4D) is gaining further acceptance in the diagnosis of myocarditis. Monoclonal antibodies allow the characterization and localization of the mononuclear cell infiltrates: for example, CD3 for T cells, PGM1 (CD68) for activated macrophages, and human leukocyte antigen (HLA)-DR- α to assess HLA class II

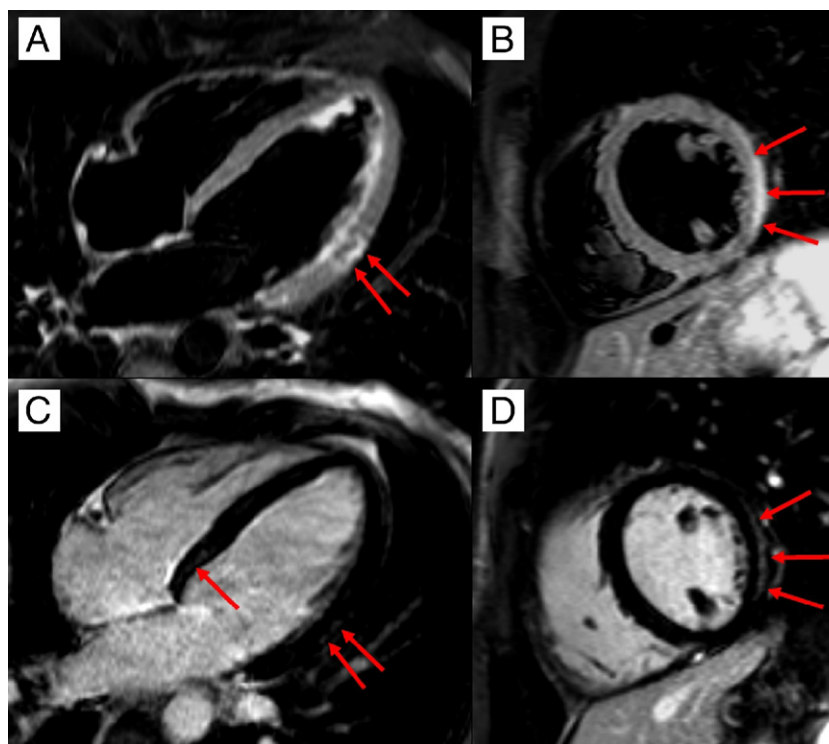


Figure 3 MRI Findings in Patients With Myocarditis

Cardiac magnetic resonance imaging (MRI) images of a young patient presenting with acute chest pain syndrome due to acute myocarditis. **(A)** Long-axis and **(B)** short-axis T2-weighted edema images demonstrating focal myocardial edema in the subepicardium of the left midventricular lateral wall (red arrows). Corresponding **(C)** long-axis and **(D)** short-axis T1-weighted late gadolinium enhancement images demonstrate presence of typical late gadolinium enhancement in the subepicardium of the left midventricular lateral wall and the basal septum (red arrows).

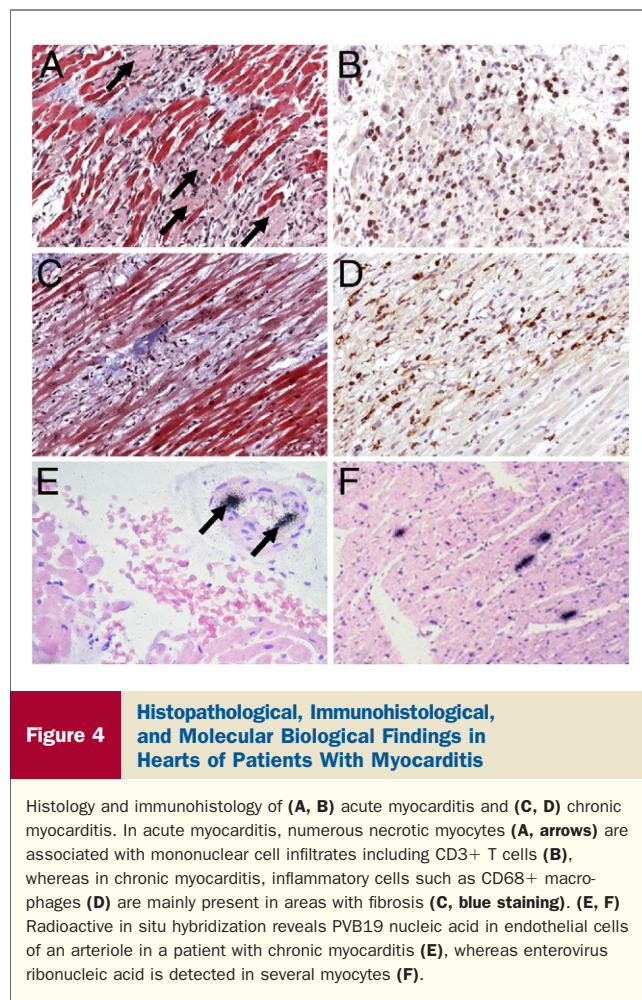
expression in professional antigen-presenting immune cells (26). With the use of these immunohistological methods the number of EMB revealing myocarditis markedly increased (46). According to the World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, EMB is considered to be inflamed by immunohistochemical detection of focal or diffuse mononuclear infiltrates (T lymphocytes and macrophages) with >14 cells/mm², in addition to enhanced expression of HLA class II molecules (1). Molecular biological detection of cardiotropic viruses can be performed by nested PCR/real time-PCR from EMB (47). In situ hybridization techniques allow the identification of cell types replicating viral genomes as shown for PVB19 and enterovirus in Figures 4E and 4F. Because of the lack of available facilities and clinical experience, EMB appears to be infrequently used to diagnose myocarditis. However, when performed by experienced interventionalists, left and right ventricular EMB are safe procedures, with a major complication rate of $<1\%$ (48). Recent studies demonstrated not only the diagnostic but also the prognostic value of EMB in patients with suspected myocarditis (4).

Treatment of Myocarditis

Although treatment of myocarditis should be focused on the causal pathophysiology, the effect of a specific causative therapy has only been confirmed in a few studies on inflammatory heart diseases such as sarcoidosis and giant cell myocarditis. Because of the high incidence of LV dysfunction, evidence-based HF therapy is mandatory in these patients. As no clinical trials of HF therapy in patients with myocarditis have been performed, only data from animal models can be consulted.

Specific treatment. Specific types of myocarditis based on autoimmunity are treated with immunosuppression, for example, in patients with giant cell myocarditis or cardiac sarcoidosis. In case of giant cell myocarditis, combined treatment with immunosuppressants (cyclosporine and corticosteroids with or without azathioprine or muromonab-CDs) may improve the poor prognosis, and yield a median survival time of 12 months compared with 3 months for untreated affected patients (18,49). Nevertheless, a minority of patients require mechanical circulatory support or heart transplantation within 1 year.

Withdrawal of immunosuppression can result in recurrent and sometimes fatal giant cell myocarditis. In case of



cardiac sarcoidosis, early immunosuppressive therapy with high-dose corticosteroids has been associated with improved cardiac function (17). The prognosis of patients with treatment is variable, with a 5 year survival ranging from 60% to 90% (50). Specific treatment options for viral myocarditis are not established yet.

Heart failure therapy. As no pathogen-specific therapy of viral myocarditis has been shown to improve survival free of HF, for now treatment is symptomatic and based on the clinical presentation. Fortunately, most cases of myocarditis are mild (21,51,52). Pharmacological treatment of HF should be initiated according to the current guidelines (53). Standard HF regime including beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) should be initiated according to the New York Heart Association (NYHA) functional class.

ACE INHIBITORS AND ARBS. By early initiation of renin-angiotensin blockade, chronic maladaptive cardiac remodeling can be attenuated, and the progression to dilated cardiomyopathy can be reduced. In mice models, the ACE inhibitor captopril as well as the ARBs losartan and olmesartan significantly reduced inflammation, necrosis, and fibrosis in experimental autoimmune or virus-induced myocarditis (54–57).

In rats with DCM caused by experimental autoimmune myocarditis, olmesartan treatment significantly improved left ventricular function and ameliorated the progression of cardiac remodeling (58). Treatment with different ACE inhibitors and ARBs in animal models may also down-regulate the potential autoimmune component of the disease without increasing the levels of the infectious agents that may have initiated myocarditis (59).

DIURETICS. Diuretics are used to prevent or to treat fluid overload. Torsemide reduced the progression of myocarditis to DCM in a rat model of inflammatory cardiomyopathy by decreasing fibrosis, myocyte sizes, and myocardial protein levels of transforming growth factor-beta-1, collagen III, and aldosterone synthase, beyond its renal effects (60).

BETA-BLOCKERS. Beta-blocker treatment should be avoided in the acute phase of decompensated HF and in the very early treatment of fulminant myocarditis (53). Beta-blockade improves ventricular function, reduces hospital admission for worsening HF, and increases survival. Experimental data suggest that the type of beta-blocker has an impact in inflammatory cardiomyopathy. Carvedilol was shown to be cardioprotective in rats with autoimmune myocarditis by suppression of inflammatory cytokines and its antioxidant properties, whereas metoprolol and propranolol were not (61). Metoprolol administration exerted deleterious effects in acute murine coxsackievirus B3 myocarditis showing significantly increased inflammation and necrosis as well as mortality compared to the placebo group (62). However, the underlying mechanism was not identified. In encephalomyocarditis virus inoculated mice, administration of epinephrine exacerbated myocarditis and increased mortality whereas treatment with propranolol decreased myocardial necrosis and infiltration of inflammatory cells as well as gene suppression of tumor necrosis factor-alpha, IL-6, and IL-10. Consequently, a reduced severity of myocarditis and a decreased mortality resulted. In patients with suspected myocarditis, there is evidence that lack of beta-blocker treatment is associated with poor outcome (4).

ALDOSTERONE ANTAGONISTS. Administration of aldosterone antagonists is recommended for systolic HF patients with persistent NYHA functional class II to IV symptoms. Aldosterone antagonists reduced hospital admission for worsening HF and increased survival in addition to established HF therapy (53). Anti-inflammatory effects of eplerenone on murine viral myocarditis were shown by inhibition of mast cell-derived proteinases and resulted in an improvement of myocardial remodeling by suppressing fibrosis (63).

CARDIAC GLYCOSIDES. Cardiac glycosides reduced morbidity in patients with symptomatic systolic HF in NYHA functional class II to IV. High doses of digoxin increased myocardial production of pro-inflammatory cytokines and worsened myocardial injury in virus-infected mice (64). Digoxin may limit the maximal tolerated dose of beta-blocker due to bradycardia or heart block. Therefore,

digoxin should be avoided in patients suffering from acute HF induced by viral myocarditis.

CALCIUM-CHANNEL BLOCKERS. Calcium-channel blockers are not generally recommended in the management of acute HF (53). However, in a murine model of congestive HF induced by viral myocarditis, amlodipine appeared to have a protective effect against myocardial injury in mice by inhibition of over-production of nitric oxide (65). The effects of pranidipine versus amlodipine were analyzed in rats with HF induced by autoimmune myocarditis. Pranidipine and amlodipine ameliorated the progression of left ventricular dysfunction and cardiac remodeling (66).

Nonsteroidal anti-inflammatory drugs and colchicine. Nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are applied for anti-inflammatory treatment of pericarditis (67) as a “nonspecific” anti-inflammatory therapy, whereas there is no indication for application in patients with myocarditis. In murine models of acute viral myocarditis, indomethacin and NSAIDs increased inflammation and mortality (68,69). Therefore, NSAIDs in the lowest required dose are reserved for patients with perimyocarditis in whom LV function is clearly normal and have prominent chest pain from pericarditis.

Physical activity. In acute myocarditis, avoidance of aerobic physical activity is indicated in addition to pharmacological therapy (70,71). In a murine model of coxsackievirus B3 myocarditis, sustained exercise increased mortality and induced a suppression of T lymphocytes (72). Myocarditis is a relevant cause of sudden death in young athletes (73,74). In 2005, the 36th Bethesda Conference Task Forces recommended that athletes with probable or definite evidence of myocarditis should be withdrawn from all competitive sports for at least 6 months and may return to training and competition if LV function and cardiac dimensions have returned to normal and if there are no clinically relevant arrhythmias (74). The duration of abstinence from competitive sports after recovery from acute myocarditis is still a matter of debate. In patients with stable HF after previous history of myocarditis, physical exercise is recommended (70).

Pacemaker and implantable cardiac defibrillator. Temporary pacemaker insertion is indicated for patients with acute myocarditis who present with symptomatic atrioventricular (AV) block II or III. Lyme carditis patients can have varying degrees of AV conduction abnormalities (75). Persistent AV block III is rare, but necessitates permanent pacing. In Chagas disease, conduction defects with a progression to complete heart block, and life-threatening ventricular arrhythmias are common (11). Because of dyssynchrony, chronic right ventricular pacing should be avoided in patients with restricted LV function, and implantation of a biventricular pacemaker should be considered (76). Insertion of an implantable cardiac defibrillator (ICD) in patients with myocarditis is indicated after cardiac arrest due to ventricular fibrillation or after symptomatic ventricular

tachycardia. Cardiac resynchronization therapy with defibrillator function is indicated for patients with impaired LV function (LV ejection fraction $\leq 35\%$) and left bundle branch block in NYHA functional class II to IV (76). However, premature implantation of an ICD or a cardiac resynchronization therapy/ICD system should be avoided in patients with inflammatory cardiomyopathy as LV function may improve significantly with guideline-based HF therapy.

Because of the worse prognosis, pacemaker or ICD implantation may be considered early in patients with sarcoidosis or giant cell myocarditis, if second- or third-degree AV block or ventricular arrhythmias have been documented (17,18).

Mechanical circulatory support, heart transplantation. For patients with cardiogenic shock due to acute fulminant myocarditis who deteriorate despite optimal medical treatment, mechanical circulatory support or extracorporeal membrane oxygenation may be required to bridge the patient to recovery or heart transplantation (27). Despite the severe initial presentation, these patients have a good prognosis, with $>60\%$ to 80% survivors and a high rate of recovery of native ventricular function (77,78). Aggressive therapy with mechanical circulatory support systems is warranted and should be considered early for patients with fulminant acute myocarditis when maximal pharmacological therapy failed.

Investigational treatment options. Because mechanism-based therapy of myocarditis is not proven, different approaches have been investigated in clinical studies in recent years. More than 20 treatment trials have been reported, using immunosuppressive, immunomodulating, or anti-inflammatory agents as well as immunoadsorption therapy (Tables 2 and 3). Immunosuppressive therapy has been evaluated in the trials listed in the following text, and in many smaller studies, but has not become a standard in therapy of inflammatory cardiomyopathy. One of the largest randomized, controlled treatment trials, the Myocarditis Treatment Trial (79), failed to show a benefit from immunosuppressive therapy additional to HF therapy. There was neither a difference in mortality nor an improvement of LV ejection fraction after 1 year of treatment with prednisone with either azathioprine or cyclosporine versus placebo. These results might be due to a lack of consensus in interpretation of EMB findings. However, no immunohistology for the detection of inflammatory cells and no molecular biological analyses of EMB were used for the detection of infectious agents. Thereby, patients with cardiac viral infection might have been treated with immunosuppressive agents, which could have increased virus replication and damaged the myocardium.

The majority of treatment studies used the Dallas criteria for histological classification of EMB. As mentioned in the preceding text, there is an ongoing debate indicating that the Dallas criteria are not suitable for the diagnosis of this inflammatory disease because of the variation in histological interpretation and the inability of detection of noncellular mediated inflammation (45). Intermediate data from the

Table 2 Treatment Trials of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy, Randomized Controlled Studies

Clinical Trial Name, Year of Publication, First Author (Ref. #)	Design, Subjects, Treatment	Results	Evaluation
Prednisone in idiopathic DCM, 1989, Parrillo et al. (90)	Single center, prospective, randomized, placebo controlled; 102 patients with idiopathic DCM with inflammatory features; treatment with prednisone or placebo.	Mean EF increased by $4.3 \pm 1.5\%$ in the prednisone group, compared to $2.1 \pm 0.8\%$ in the control group ($p < 0.054$).	Benefit
European study of epidemiology and treatment of inflammatory heart disease (ESETCID), 1995, Hufnagel et al. (80)	Multicenter, double-blind, randomized, placebo controlled; pooled subgroup analysis; 182 patients with biopsy-proven acute or chronic myocarditis and LVEF $<45\%$. Cytomegalovirus-induced myocarditis treated with hyperimmunoglobulin. Enterovirus-positive myocarditis treated with interferon alpha. Adenovirus-positive myocarditis treated with IgG and IgM immunoglobulin. Virus-negative myocarditis, considered autoimmune, treated with immunosuppressive therapy (prednisolone and azathioprine). All groups compared to placebo.	Inflammation was eliminated in 59% of patients in treatment group and 40% in placebo group.	No benefit
Interferon and thymic hormones in the therapy of human myocarditis and idiopathic DCM, 1996, Miric et al. (95)	Single center, randomized, open label, not blinded; pooled treatment group analysis; 38 patients with EMB-proven myocarditis or DCM: 12 patients treated conventionally, 13 treated with interferon-alpha and conventional treatment, and 13 with thymomodulin and conventional treatment.	LVEF improved in 21 (81%) of 26 patients after interferon-alpha or thymomodulin and in 8 (66%) of 12 conventionally treated patients ($p < 0.05$) at 2-year follow-up.	Benefit
Myocarditis treatment trial, 1995, Mason et al. (79)	Multicenter, randomized, controlled trial; 111 patients with myocarditis and LVEF $<45\%$; conventional therapy alone (group 1) or combined immunosuppressive therapy with prednisone plus cyclosporine or azathioprine (group 2); pooled treatment group analysis.	No difference in survival between 2 groups ($p = 0.96$); mean change in LVEF at 28 weeks did not differ significantly between the 2 groups.	No benefit or harm
Immunomodulation therapy with IVIG in patients with chronic heart failure, 2001, Gullestad et al. (96)	Randomized, placebo-controlled, double-blind trial; 40 patients with chronic DCM or ICM. Therapy with IVIG vs. placebo. Primary endpoint LVEF change at 6 months.	IVIG, but not placebo, induced marked rise in plasma levels of anti-inflammatory mediators IL-10, IL-1 receptor antagonist, and soluble TNF receptors; IVIG, but not placebo, induced significant increase in LVEF from $26 \pm 2\%$ to $31 \pm 3\%$ ($p < 0.01$).	Benefit at 6 months, not sustained at 12 months
Intravenous immune globulin in recent-onset dilated cardiomyopathy or myocarditis, 2001, McNamara et al. (82)	Multicenter, double-blinded, randomized, controlled study; 62 patients with recent-onset (6 months) heart failure and unexplained DCM; therapy with intravenous immune globulin vs. placebo.	Overall LVEF improved, 0.25 ± 0.08 to 0.41 ± 0.17 at 6 months ($p < 0.001$) and 0.42 ± 0.14 ($p < 0.001$ vs. baseline) at 12 months; increase identical in patients given IVIG and patients given placebo.	No benefit
Immunosuppressive treatment of inflammatory dilated cardiomyopathy, 2001, Wojnicz R et al. (89)	Randomized, placebo-controlled, not blinded; 84 patients with DCM, symptoms >6 months, and increased HLA expression in myocardium; immunosuppressive therapy with prednisolone and azathioprine vs. placebo.	No significant difference in primary endpoint (composite of death, heart transplantation, and hospital readmission) between the 2 study groups (22.8% for immunosuppression; 20.5% for placebo); LVEF increased and LV systolic diameter decreased.	Equivocal benefit
Immunosuppressive therapy in patients with virus negative inflammatory cardiomyopathy (TIMIC study), 2009, Frustaci et al. (91)	Randomized, double blind, placebo controlled; 85 patients with biopsy-proven virus negative inflammatory cardiomyopathy; prednisone and azathioprine for 6 months (group 1) or placebo (group 2).	Group 1, significantly improved LVEF and decreased LV dimensions; Group 2, none showed improved LVEF.	Benefit

DCM = dilated cardiomyopathy; EF = ejection fraction; EMB = endomyocardial biopsy; HLA = human leukocyte antigen; ICM = ischemic cardiomyopathy; IL = interleukin; IVIG = intravenous immunoglobulin; LV = left ventricle; LVEF = left ventricular ejection fraction; TNF = tumor necrosis factor.

ESETCID (European Study of Epidemiology and Treatment of Inflammatory Heart Disease) study (80) showed that inflammation was eradicated in 59% of the patients treated with immunosuppressive agents; however, it also vanished spontaneously in 40% of the placebo group. The high rate of spontaneous improvements in patients with acute inflammatory cardiomyopathy (81) is not considered

in many treatment trials. To detect modest (but real) differences in treatment, further placebo controlled treatment studies are needed to reduce this major limitation in therapy assessment. The validity of the listed trials is limited by there frequently being no adequate immunohistological and molecular biological analysis of EMB, and in several trials, no control groups were implemented.

Table 3 Treatment Trials of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy, Nonrandomized Controlled/Uncontrolled and Randomized Uncontrolled Studies

Clinical Trial Name, Year of Publication, First Author (Ref. #)	Design, Subjects, Treatment	Results	Evaluation
Interferon beta in patients with myocardial persistence of viral genomes and LV dysfunction, 2003, Kühl <i>et al.</i> (6)	Phase II study, not blinded, single center, no control group; 22 patients with mild LV dysfunction and PCR-proven enteroviral or adenoviral infection of myocardium; treatment with 18×10 IU/week IFN-beta (Betaferon) subcutaneously for 24 weeks.	Virus clearance paralleled by significant LVEDD and LVESD decreases, from 59.7 ± 11.1 mm to 56.5 ± 10.0 mm ($p < 0.001$) and 43.2 ± 13.6 mm to 39.4 ± 12.1 mm ($p < 0.001$). LVEF increased from 44.6 ± 15.5% to 53.1 ± 16.8% ($p < 0.001$); viral genome elimination observed in all patients after antiviral therapy.	Benefit
Immunosuppressive therapy for active lymphocytic myocarditis, 2003, Frustaci <i>et al.</i> (97)	Single center, retrospective analysis; 112 patients with histological diagnosis of active lymphocytic myocarditis, 41 of these had progressive heart failure despite conventional therapy; treatment with prednisone and azathioprine.	Patients with circulating cardiac autoantibodies and no viral genome benefit from immunosuppression therapy; 21 patients had improved LVEF from 25.7 ± 4.1% to 47.1 ± 4.4%.	Benefit for patients with circulating cardiac antibodies and no virus in myocardium
Intravenous immunoglobulin (IVIG) therapy for patients with idiopathic cardiomyopathy and EMB-proven high PVB19 viral load, 2010, Dennert <i>et al.</i> (98)	Not blinded; 17 patients with DCM and symptomatic heart failure for >1 yr with PVB19 viral load in EMB of >250 copies/μg DNA; treatment with high-dose IVIG.	IVIG therapy resulted in significant decrease of PVB19 viral load from 1,420 ± 216 to 619 ± 200 copies/μg DNA ($p = 0.004$); LVEF improved significantly from 34 ± 3% at baseline to 41 ± 3% at 6 months ($p = 0.001$) after IVIG therapy.	Benefit
Children with myocarditis treated by immunosuppression and of children with DCM, 2004, Gagliardi <i>et al.</i> (99)	Single center, nonrandomized cohort; 114 patients: group A: acute myocarditis; group B: borderline myocarditis; group C: noninflammatory cardiomyopathy. Groups A and B treated with cyclosporine and prednisone plus conventional treatment; group C given conventional treatment.	Cardiac function recovered completely in 79% of survivors in group A, 64% in group B, and 36% in group C.	Benefit
Effect of protein A immunoadsorption on T-cell activation in patients with inflammatory DCM, 2010, Bulut <i>et al.</i> (88)	Single center; 10 patients with chronic inflammatory DCM (with signs of myocardial inflammation in EMB but no persistence of virus genome and reduced LVEF [$<35\%$]); therapy with IA.	LVEF improved from 25.6 ± 4.9% to 37.3 ± 10.1% ($p < 0.05$) after 6 months; LVEDD reduced after 6 months (63.3 ± 3.1 mm vs. 57.1 ± 4.1 mm; $p < 0.05$).	Benefit
Immunoadsorption and subsequent immunoglobulin G substitution in patients with DCM, 2010, Herda <i>et al.</i> (86)	Single center university hospital-based case-control; 60 patients with DCM (NYHA II–IV, LVEF ≤45%); therapy with or without IA/IgG.	LVEF improved significantly in IA/IgG-treated group from 33.0 ± 1.2% to 40.1 ± 1.5% ($p < 0.001$).	Benefit
Removal of cardiodepressant antibodies in DCM by immunoadsorption (IA) (87), 2002, Felix <i>et al.</i> (84)	Multicenter, double-blind, prospective; 11 patients with DCM; IA on 3 consecutive days; IA also conducted on 500 ml blood from 9 healthy donors (control subjects).	IgG plasma level decreased from 10.7 ± 0.6 g/l to 2.4 ± 0.1 g/l and the cardiac index increased from 2.2 ± 0.1 l/min/m ² to 2.7 ± 0.2 l/min/m ² ($p < 0.01$).	Benefit
Immunoadsorption (IA) in DCM, 2006, Staudt <i>et al.</i> (100)	Randomized, uncontrolled; 22 patients with heart failure (LVEF <35%) due to DCM; group 1 ($n = 11$) treated with 4 IA courses at monthly intervals; group 2 ($n = 11$) received 1 IA course only without repetition.	Group 1, improved LVEF after 6 months, from 28.1 ± 1.5% to 37.0 ± 1.6% ($p < 0.01$); cardiac index increased from 2.2 ± 0.1 l/min/m ² to 2.8 ± 0.2 l/min/m ² after 6 months ($p < 0.01$); group 2, comparably improved LVEF at 6 months, from 26.5 ± 2.2% to 34.8 ± 2.9% ($p < 0.01$). Cardiac index increased from 2.1 ± 0.1 l/min/m ² to 2.7 ± 0.2 l/min/m ² .	Benefit
Effects of protein A immunoadsorption in patients with advanced chronic DCM, 2009, Doesch <i>et al.</i> (85)	Single center; 27 patients with DCM, congestive heart failure NYHA class ≥II, LVEF <40%; therapy with IA.	Mean LVEF not significantly improved at 6 months (24.1 ± 7.8% to 25.4 ± 10.4%, $p = 0.38$); LVEF improved (≥5% absolute) in 9 of 27 (33%) patients; bicycle spirometry showed significant increase in exercise capacity from 73.7 ± 29.4 W to 88.8 ± 31.1 W ($p = 0.003$) after 6 months; VO ₂ max increased from 13.7 ± 3.8 ml/min/kg to 14.9 ± 3.0 ml/min/kg ($p = 0.09$).	No benefit in LVEF, but in exercise capacity

DNA = deoxyribonucleic acid; IA = immunoadsorption; IFN = interferon; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NYHA = New York Heart Association; PCR = polymerase chain reaction; other abbreviations as in Table 2.

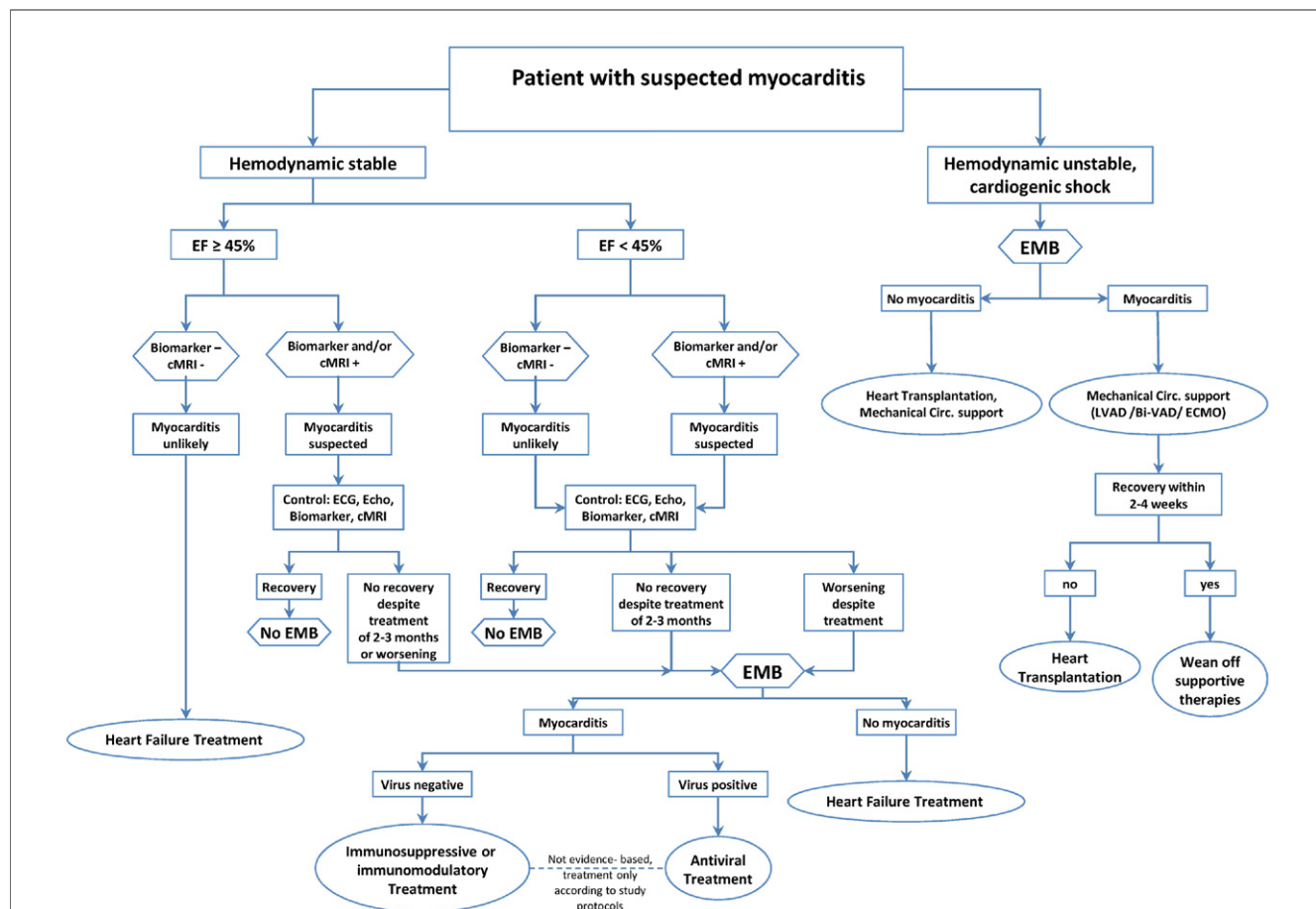


Figure 5 Proposed Diagnostic and Therapeutic Algorithm for Suspected Myocarditis

Proposed diagnostic and therapeutic algorithm for patients with suspected acute myocarditis considering biomarkers, cardiac magnetic resonance imaging (cMRI), and endomyocardial biopsy (EMB). Bi-VAD = biventricular assist device; Circ. = circulatory; ECMO = extracorporeal membrane oxygenation; LV = left ventricular; LVAD = left ventricular assist device.

An algorithm outlining a proposed diagnostic and therapeutic approach in patients with suspected myocarditis is pictured in Figure 5.

IMMUNOGLOBULIN TREATMENT. The rationale to use immunoglobulin in viral myocarditis results from their antiviral and immunomodulating effects. In recent onset of myocarditis or DCM, there was no difference in LV function in patients receiving intravenous immunoglobulin and patients given placebo (82). However, children with acute myocarditis showed an improvement of LV function and survival in the first year after treatment (83).

IMMUNOADSORPTION. The target of immunoadsorption is the elimination of anticardiac antibodies against various cardiac cell proteins, which have been identified in patients with DCM and myocarditis (84). There is evidence that removal of circulating antibodies by immunoadsorption in DCM improved cardiac function (84) and clinical and humoral markers of HF severity (exercise capacity, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) [85,86]) as well as hemo-

dynamic parameters (cardiac and stroke volume index, systemic vascular resistance) (87). Furthermore, immunoadsorption decreased myocardial inflammation (85). In patients with inflammatory cardiomyopathy, LV systolic function improved after protein A immunoadsorption (88). Currently a multicenter, randomized, double-blind, prospective study on the effects of immunoadsorption on cardiac function in 200 patients with DCM is ongoing (NCT00558584). First results are expected in 2011 and 2012.

IMMUNOSUPPRESSIVE TREATMENT. Treatments with immunosuppressive agents (cyclosporine, prednisolone, azathioprine) in acute myocarditis have shown controversial results (Tables 2 and 3) (79,80). In chronic DCM, azathioprine and prednisone resulted in an improvement of LV function and NYHA class (89,90). The TIMIC (Immunosuppressive Therapy in Patients With Virus Negative Inflammatory Cardiomyopathy) study (91) was the first randomized, placebo-controlled trial in which all EMB were studied for inflammation by histological and immunohisto-

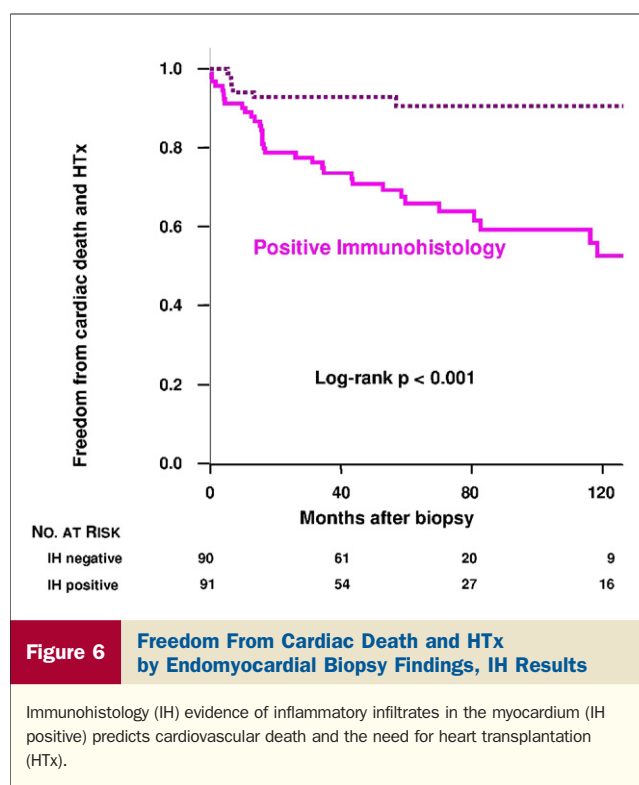
logical criteria. Molecular biological analyses were performed in all biopsy specimens to exclude viral infection. A significant improvement of LV ejection fraction and a decrease in LV dimensions resulted from immunosuppressive therapy with prednisone and azathioprine.

ANTIVIRAL TREATMENT. The rationale to use antiviral drugs results from the knowledge that most common cases of myocarditis are induced by viral infections. In murine coxsackievirus B3-induced myocarditis, interferon (IFN)-beta and IFN-alpha2 therapy protected myocytes against injury and decreased inflammatory cell infiltrates. However, only IFN-beta resulted in an elimination of cardiac viral load (92). Treatment with IFN-beta in patients with myocardial enteroviral or adenoviral persistence and LV dysfunction showed an elimination of viral genomes in all patients and an improvement of LV function in 15 of 22 patients (6). In the subsequent placebo-controlled, randomized, double-blind, Europe-wide multicenter BICC (Betaferon in patients with chronic viral cardiomyopathy) study, 143 patients with inflammatory DCM and confirmed myocardial viral infection were treated with Betaferon (IFN-beta-1b) versus placebo (93). Treatment with Betaferon reduced significantly viral load (enteroviruses) in the myocardium; however, complete viral elimination (PVB19) was not achieved in all patients. A variety of parameters were evaluated, but only the NYHA functional class and patient global assessment improved.

Prognosis and Outcome

The prognosis of patients with myocarditis depends on clinical presentation, different clinical parameters, and EMB findings. Patients with acute myocarditis and preserved LV ejection fraction have a good prognosis with a high rate of spontaneous improvement without sequelae (36). Patients with fulminant viral myocarditis and hemodynamic compromise at presentation have an excellent long-term prognosis and are more likely to experience complete recovery than patients with acute myocarditis (81), if aggressive pharmacological and/or mechanical circulatory support is initiated early during the fulminant phase. In patients with cardiac sarcoidosis or giant cell myocarditis, prognosis depends probably on an early initiated treatment (immunosuppressive therapy or heart transplantation).

Among clinical markers NYHA functional class, right ventricular dysfunction, elevated pulmonary artery pressure, and syncope are able to predict survival free from cardiac death or heart transplantation (36). Other clinical risk factors in patients with suspected myocarditis are low systolic, diastolic, and mean arterial blood pressures as well as high heart rate, as demonstrated by Mahfoud *et al.* (in review). A prolonged QRS duration ≥ 120 ms has also been shown to predict for cardiac death or heart transplantation in patients with suspected myocarditis (35).



The prognostic value of EMB findings has been long controversial because of the lack of specific treatment options (48). Since 2007, a consensus statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology recommends EMB in patients with suspected specific myocardial disorders with unique prognosis and specific treatment recommendations (94).

Further studies to investigate the utility of novel tools for the analysis of EMB were recommended. In a study by Kindermann *et al.* (4), the prognostic role of EMB, with detailed analysis of myocardial specimens including immunohistochemical staining for characterization of inflammation and molecular pathological analysis for detection of viral genome, was examined in 181 patients with suspected myocarditis. Immunohistological evidence of inflammatory infiltrates in the myocardium (with or without evidence of viral genome detection) was demonstrated to predict cardiovascular death and the need for heart transplantation (Fig. 6). Neither the histopathological Dallas criteria nor the detection of viral genome was a predictor of poor outcome. A risk stratification approach based on biopsy results, clinical findings, and drug treatment demonstrated that patients in NYHA functional class III or IV with positive immunohistology and without beta-blocker therapy have the poorest prognosis, with a 5-year transplantation-free survival rate of only 39% (Fig. 6).

Conclusions

Myocarditis is an under-diagnosed cardiac disease resulting from a broad range of infectious, immune, and toxic causes.

Affected patients may recover, develop DCM, or die. Although remarkable advances in diagnosis, understanding of pathophysiological mechanisms, and treatment of myocarditis have been achieved during the last years, standard treatment strategies remain limited to evidence-based HF therapy in the most cases. Immunomodulating and immunosuppressive therapy have been effective, particularly in a single-center trial (TIMIC study), only in chronic, virus-negative inflammatory cardiomyopathy. Immunosuppression therapy is beneficial for acute giant cell myocarditis and sarcoidosis, and for patients with acute myocarditis associated with autoimmune diseases, for example, lupus myocarditis. There is some evidence that antiviral therapies and antimicrobial agents may have a beneficial therapeutic effect, but controlled, adequately powered, randomized studies are needed to determine their role in treatment of myocarditis.

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