Definition and etiology
Myocarditis refers to the clinical, imaging, biochemical and histological manifestations of myocardial inflammation. The cardinal feature of myocardial inflammation is an abnormally high number of effector lymphocyte subsets and macrophages associated with myocyte damage. The clinical syndromes associated with myocarditis include myopericarditis, sudden death and heart failure resulting from immune-mediated myocardial damage. Common findings in myocarditis include stiffening and contractile impairment of the ventricles, conduction system disease and a heightened risk of ventricular arrhythmias, particularly during exercise.

The histological definition of myocarditis is classically represented by the Dallas criteria, proposed by a consensus panel of cardiovascular pathologists in 1986 [1]. These criteria define myocarditis as an inflammatory cellular infiltrate in the heart with or without myocyte necrosis and/or degeneration of adjacent myocytes. In the past two decades immunohistochemical criteria that include the increased expression of class II (HLA-DR) anti-human leukocyte antigens and heightened numbers of CD3, CD4, CD8 or CD68-positive inflammatory cells have increased the sensitivity of endomyocardial biopsy (EMB) for the diagnosis of myocarditis [2]. Markers of complement deposition that are commonly seen in humeral allograft rejection have recently been found in patients with cardiomyopathy, suggesting persistent activation of innate immune pathways [3].

Myocarditis may result from a myriad of cardiac infections and noninfectious triggers such including toxins, chest irradiation and rarely even vaccines [4]. In the setting of systemic inflammation myocarditis can...
develop in association with autoimmune disorders such as lupus erythematosus, hypersensitivity reactions or idiopathic hypereosinophilic syndrome [5, 6]. The most commonly identified cause of myocarditis is an upper respiratory tract or gastrointestinal virus infection. The most common viruses identified in heart biopsies from patients with acute myocarditis are currently parvovirus B19 and human herpes virus 6 [7]. Because most data on viral cardiomyopathy were gathered from case series in Europe and North America, the prevalence of viral disease as a proportion of heart failure in much of Africa, Asia and South America remains unknown. In specific regions of the developing world, rheumatic carditis after streptococcal A infection and Chagas’ disease from Trypanosoma cruzi remain important causes of myocarditis and heart failure [8].

Pathogenesis
The pathogenesis of myocarditis can be simplified into a phase of acute injury, a subsequent innate and adaptive immunological response and finally a transition either to chronic cardiomyopathy with fibrotic scar or to recovery (Figure 1) [9]. Genetic factors strongly impact susceptibility to and outcome of myocarditis in mice, but specific genes that influence human disease have not been identified [10]. In enteroviruses, variations in the 5’ region of the viral genome influence replication efficiency and virulence [11].

In models of enteroviral myocarditis, virus-mediated acute myocyte damage elicits an innate immune response that includes the recruitment of natural killer cells and proinflammatory cytokines through an inflammasome-mediated pathway [12]. The innate response develops into an antigen-specific immune response, which leads to successful virus clearance. In many cases the immune reaction downregulates and immune homeostasis is restored with no lasting cardiac damage. However, in a minority of cases the virus and/or the inflammatory reaction persists and contributes to cardiomyopathy and a syndrome of heart failure. Up to 30% of myocarditis cases progress to chronic cardiomyopathy [13]. Autoantigens such as cardiac myosin can mediate this chronic myocardial damage through molecular mimicry with viral antigens [14]. The opportunity for therapeutic intervention in clinical medicine is presently limited to the later phases of this disease model.

Management
In 2013 the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases published a position statement on the management and therapy of myocarditis [15]. In their paradigm, management of patients who have persistent cardiomyopathy resulting from acute myocarditis depends on the presence or absence of myocardial infection and inflammation. Patients with viral infection may be considered for antiviral therapies. Patients with inflammation and no virus infection may benefit from immunosuppressive or immunomodulatory therapies [16]. Patients with neither evidence of viral genomes nor inflammation and whose ejection fraction is less than 40% should be treated with guideline-based heart failure therapy. An EMB is required to determine whether inflammation or infection is present.

The ESC position statement recommends that a standard 12-lead ECG and a transthoracic echocardiogram be performed in all patients with clinically suspected myocarditis. Although there are no ECG changes sufficiently specific to diagnose myocarditis, the presence of QRS prolongation is an independent negative predictor of survival [17]. The echocardiogram is valuable to exclude valvular or pericardial heart disease. Echocardiographic findings predictive of lower transplant-free survival are lower left ventricular ejection fraction and impaired right ventricular function [18].

Myocardial damage occurs in about a third of patients with pericarditis [19]. In patients with pericarditis, a troponin rise and normal left ventricular function the term “myopericarditis” is used. In patients with pericarditis and more severe myocardial dysfunction, the term “perimyocarditis” has been suggested. The overall likelihood of death or heart failure is quite low in patients with myopericarditis [20]. Non steroidal anti-inflammatory drugs and colchicine are probably safe for the treatment of pericarditis even with elevated troponin if the ejection fraction is normal, but should be avoided in more severe cases with systolic heart failure.

Abbreviations
ACCF/AHA: American College of Cardiology Foundation/American Heart Association; DCM: dilated cardiomyopathy; EMB: endomyocardial biopsy; ESC: European Society of Cardiology; 18FDG: [18F]2-fluoro-2-deoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography.
Avoidance of competitive athletics is recommended in all patients with myocarditis and myopericarditis for at least 6 months. Return to athletics requires re-evaluation of heart function and an assessment of arrhythmic risk usually with a Holter monitor and/or an exercise ECG [21].

Cardiac magnetic resonance imaging (MRI) is useful to distinguish ischemic from nonischemic...
cardiomyopathy. An expert panel recommended that both T1 and T2-weighted imaging be used to obtain optimal sensitivity and specificity when myocarditis is suspected [22]. When gadolinium contrast imaging is not feasible, T1 mapping is an emerging tool that can be used as a criterion for the detection of acute myocarditis with a reported sensitivity of 91% [23].

Radionuclide imaging in unexplained cardiomyopathy is limited to several uncommon clinical scenarios. Resting perfusion imaging combined with $^{18}$FDG-2-fluoro-2-deoxyglucose ($^{18}$FDG) positron emission tomography (PET) can be helpful in the diagnosis of cardiac sarcoidosis. $^{18}$FDG uptake is increased in myocardial granulomas in regions with a matched decrease in perfusion. In regions of scar from previous inflammation, a matched decrease in $^{18}$FDG and perfusion tracers in a non coronary distribution may be seen. Extrathoracic sites of active sarcoidosis and changes in $^{18}$FDG uptake following immunosuppression can also be tracked with PET imaging [24].

Mechanical circulatory support with ventricular assist devices or extracorporeal membrane oxygenation support is beneficial as a bridge to transplantation or recovery in adults and children with fulminant myocarditis and profound shock [25]. Cardiac transplantation is also an effective therapy for patients with myocarditis who have refractory heart failure, and survival after transplantation is similar to survival in adults for other causes of cardiac transplantation [26]. The outcome following transplantation in children may be worse than for other causes of dilated cardiomyopathy (DCM) if myocarditis is the cause of transplantation [27].

The role of transvenous EMB in the management of cardiomyopathy remains controversial. However, the 2013 position statement from the ESC Working Group on Myocardial and Pericardial Diseases and the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of heart failure disagree on the routine use of EMB in unexplained DCM [15, 28]. Histology and immunohistology are required to confirm inflammation, and viral genome analysis is a common method to infer active viral infection, but when do the data from EMB change prognosis and management?

In certain clinical scenarios, unique data from EMB will impact prognosis and therapy. Consensus generally exists that EMB-confirmed sarcoidosis will change management by the use of immunosuppressive therapy in most cases. Lymphocytic myocarditis predicts successful bridging to recovery after left ventricular assist device in adults [29] and the long-term risk of allograft rejection in children [27]. Viral genomes on EMB have been associated with increased risks of left ventricular dysfunction, heart transplantation or death [30–31]. The literature regarding the prognostic value of viral genomes to predict heart transplantation or death is mixed [32].

Since the 2013 ACCF/AHA guideline for the management of heart failure was published, a case series from Johns Hopkins Hospital reported results from 851 patients who underwent right ventricular EMB from 2000 to 2009 [33]. Overall, 25.5% of EMB provided a diagnosis and 22.7% of EMB changed the clinical course. The authors concluded that EMB is useful in acute-onset unexplained cardiomyopathy. However, the usefulness of EMB in chronic DCM was low. Recent reports suggest that left ventricular EMB has a greater diagnostic utility than right ventricular EMB in disorders that primarily affect the left ventricle [34, 35].

**Future directions**

The MRI patterns of epicardial and/or mid-myocardial signal abnormality can identify nonischemic myocarditis or scar, but neither MRI nor $^{18}$FDG PET can identify specific causes and cellular types such as giant cell or eosinophilic myocarditis. However, perfluorocarbons such as $^{19}$fluorine can specifically detect macrophages, granulocytes and dendritic cells in murine myocarditis. A recent study by van Heeswijk et al [36] demonstrated that the perfluorocarbon $^{19}$fluorine can be detected using 9.4T cardiac MRI in a mouse model of autoimmune myocarditis. Translation of this and similar imaging agents under investigation to the clinical arena should allow for the noninvasive detection of myocarditis in settings where EMB is not readily available.

Emerging therapies to prevent the progression of acute myocarditis to chronic DCM may focus on patient-specific immune reactions. For example, T helper type 17 cells are increased and T regulatory cells are decreased in mice with myocarditis [37]. The persistence of this or other immunophenotypes may identify subsets of myocarditis patients who are at risk of chronic heart failure and who may benefit from tailored immunotherapy. Clinical trials of protein A immunoadsorption, a cyclic peptide that binds anti-$\beta_1$-receptor antibodies and specific anticytokine strategy studies are underway or planned [38].
REFERENCES

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