Introduction
The term myocarditis describes inflammatory disorders of the heart muscle of varied infectious and noninfectious origin. It can be caused by any kind of infection, drugs, toxic substances, or may be associated with autoimmune conditions (Table I). Viruses are the main cause in developed countries while bacteria or other infectious agents predominate in the etiology of myocarditis in rural countries [1]. The actual incidence of virus-induced myocarditis or virus-associated cardiomyopathy is not well established because viral heart disease may not be apparent, is difficult to diagnose and can vary with different viruses as a function of circulating virus populations. Chronic myocardial inflammation may be caused by persisting organ infections, toxic agents or distinct physical conditions, may persist as a post-infectious condition, or be associated with systemic autoimmune conditions [2].

The clinical presentation of myocarditis ranges from mild “flu-like” symptoms or persisting physical disability with no hemodynamic consequences to congestive heart failure, ventricular dysfunction, arrhythmias and sudden cardiac death. In the absence of structural heart diseases myocarditis accounts for approximately 10% of recent-onset cardiomyopathy in adults and this figure may be higher in children. Early fulminant disease is still associated with a high mortality rate despite timely admission to intensive care. Patients
who survive the critical phase have a fairly good prognosis and survival from myocarditis is approximately 60–70%. In the remaining patients progressive chronic heart failure and unpredictable sudden cardiac death remain a serious concern, often occurring years after the initial clinical event and sometimes despite complete recovery of myocardial function in the meantime.

**Acute infectious myocarditis**

Etiologies of acute infectious myocarditis include viruses, protozoa, bacteria, or fungi, but often the underlying cause cannot be identified. Apart from enteroviruses, which traditionally have been considered the most common agent in myocarditis and dilated cardiomyopathy (DCM), distinct genotypes of erythroviruses including parvovirus B19 (B19V), human herpesvirus type 6 (HHV6), adenoviruses, HIV, cytomegalovirus, herpes simplex type 2 virus and hepatitis C virus, and many others have been identified with varying degrees of frequency (Table I) [3, 4]. Chagas’ disease, which can present acutely as in fulminant myocarditis, or progress insidiously into a chronic cardiomyopathy with symptomatic heart failure, is still one of the most common causes of DCM worldwide. The causative organism is the protozoa Trypanosoma cruzi, which is prevalent in endemic regions in the world, most notably in South America.

Infectious agents such as viruses are often processed in lymphoid organs and may proliferate within immune or other cells, eg, lymphocytes or macrophages. They subsequently achieve target organ infection through hematogenous or lymphangitic spread. The early phase of myocardial disease is initiated by infection of cardiac myocytes, fibroblasts, or endothelial cells through receptor-mediated endocytosis.

Enteroviruses and adenoviruses enter the heart as a secondary target organ and infect and injure cardiomyocytes after binding to the Coxsackie adenoviral receptor [5]. In contrast to such newly acquired infections, which target and injure cardiac cells at any age, B19V is acquired by the majority of patients in childhood and, due to the virus receptor distribution, persists lifelong within bone marrow and the vascular endothelial precursor cells (EPC) in more than 70% of individuals over 60 years of age [6]. Permanent infection of the vascular endothelium in adults thus does not

**Table I** Etiological agents causing myocarditis. EBV, Epstein–Barr virus; HHV6, human herpesvirus type 6; HSV, herpes simplex virus.
generally occur from newly acquired B19V infection, which constitutes a rare event in adults, but through endogenous B19V-infected bone marrow-derived endothelial progenitor cells, which are released into the bloodstream during vascular repair [7].

Similarly, HHV6 is commonly acquired during the first 2 years of life, and also persists in latent form for life. In heart tissue, HHV6 genomes are detected in vascular endothelial cells, cardiomyocytes and infiltrating interstitial cells [8]. Unique among human herpesviruses, the HHV6 genomes can furthermore become integrated into the human genome (ciHHV6) and can be transmitted by means of germline chromosomonal integration, in which they have similar prevalence and result in the potential for virus gene expression in every cell [9]. ciHHV6 affects approximately 0.2–0.8% of human populations.

At the time of the first onset of symptomatic heart disease, most common acute viral infections clinically present as myocarditis often with infarct-like presentation or unexpected onset of acute heart failure. The resulting type and extent of myocardial compromise and hence the prognosis of the disease depend on the nature of the offending infectious agent, the affected cardiac structures, and the degree of irreversible myocardial lesions caused by cytolytic viruses or the innate and adaptive anti-infectious immune responses [1, 2]. For clinical management and with respect to pathogenicity and prognosis it has to be taken into consideration that those viruses that do not infect cardiomyocytes constitute distinct disease entities at least in the short run. Therefore, despite a similar clinical and histological presentation, B19V and HHV6-associated myocarditis in adults should not be considered in the same way as newly acquired enteroviruses, adenoviruses or other cardiotropic infections that rapidly destroy contractile cardiac tissue.

Pathogenicity

For many viruses the exact cardiac infection site and the underlying pathogenic mechanisms are unknown, and most information on the distinct phases of viral heart disease is derived from enteroviral infections. Myocarditis can be considered to have three phases in its pathophysiology. The first is the viral phase, followed by the immunological response phase, followed by the cardiac remodeling phase [1, 10]. A direct virus-related cytolysis of cardiomyocytes can already be detected before any inflammatory infiltrate develops. After this enterovirus RNA is predominantly located in areas showing focal inflammatory cell infiltrates and myofibre necrosis (Figure 1(b, c)). This indicates that during early disease direct lytic infection of myocytes rather than an autoimmune reaction is responsible for myocarditis.

The innate and adaptive antiviral immune responses initiate a further step in the development of virus-associated myocarditis [1, 10]. It is activated to eliminate as many virus-infected cardiac cells as possible to control the infection [11]. In addition to the early virus-mediated injury, this immune-mediated virus clearance from infected cardiomyocytes takes place at the expense of a further destruction of myocardial tissue that is not capable of regeneration (Figure 1(c)) [12].

The antiviral immune response then has to be modulated by negative controls in order to prevent excessive tissue damage and organ dysfunction. Inflammation resolves the majority of cases (>70%) after successful virus clearance or suppression of transcriptional activation of the virus. Even after complete resolution of inflammation, however, tissue damage that has developed in the early stages may contribute to later tissue remodeling and progression of the disease (Figure 1(e, f)). The degree of remodeling of the heart following cardiac injury affects cardiac structure and function and determines the difference between appropriate healing or the development of post-infectious DCM [11, 13].

Chronic myocarditis and inflammatory cardiomyopathy

Acquired viral cardiomyopathy

A virus-associated cardiomyopathy develops if, due to an inadequate immune response, the acquired virus is not cleared successfully or if transcriptional virus activity persists. Viral persistence can expose the host to persistent antigenic trigger and chronic immune activation resulting in chronic myocarditis. A smoldering inflammatory process, characterized by diffuse low grade infiltrates of lymphocytes, macrophages and enhanced tissue expression of cell adhesion molecules, is detectable in about 40% of patients with chronic enteroviral or adenoviral infection [14]. A similar frequency and value of inflammation is also detected in the myocardial tissue of patients with B19V and HHV6 infections [15, 16]. Transcriptionally
active B19V infection is associated with an altered cardiac expression of genes that encode proteins of the antiviral immune response and mitochondrial energy metabolism [17]. This may also be responsible for prolonged B19V-associated intramyocardial inflammation and impairment of myocardial function, which, in the long run, affect the outcome of patients [7, 17]. Histologically, interstitial fibroses and scars indicate chronic myocardial alterations caused by both the persisting virus and chronic immune cell activation (Figure 1 (e, f)).

**Post-infectious chronic myocarditis**
The presentation of viral antigens that evokes an antiviral immune response, which aims at viral elimination, is not necessarily detrimental to the heart. However, this immune response is a “double-edged sword”: molecular mimicry and genetically predisposing conditions can secondarily target cryptic myocardial antigens [18]. In the case of post-viral (auto)immunity, this immune response continues despite successful elimination of the viral genome. In addition, organ-specific cellular (auto)immunity antibodies that crossreact with myocardial antigens and are cross-linked by Fc-receptors at the myocyte surface may contribute to impairment of cardiac function [19]. In addition, cardiodepressive cytokines induced by the immune system can directly impair cardiac contractility. While the pathogenic relevance of autoantibodies has been questioned in the past as epiphenomena of the immune response, recent experiments with stimulating antibodies directed against the second extracellular β1-receptor loop and positive results from immunoadsorption studies have indicated a causative role for autoantibodies in DCM.

**Noninfectious myocarditis**
Giant cell myocarditis (GCM, Figure 1 (d)), acute eosinophilic myocarditis and granulomatus inflammatory processes such as cardiac sarcoidosis are rare but clinically important acute inflammatory heart muscle diseases often of unknown etiology. The majority of patients present with acute heart failure on the first encounter. These myocarditis subtypes have a high mortality rate if not diagnosed and treated in time [2].

Many medications have been implicated in contributing to hypersensitivity myocarditis [1]. Symptomatic myocarditis with fever, skin rash, peripheral eosinophilia and sinus tachycardia can occur in an unpredictable fashion following the ingestion of a particular drug that may be new to the patient’s regimen, or that they have previously ingested and been exposed to for quite some time. Drugs may induce myocardial inflammation by either direct toxic effects on heart tissue or by inducing hypersensitivity reactions, which

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**Fig. 1** Diagnostic evaluation of inflammation in a myocardial biopsy specimen (histology and immunohistology). (a) Normal myocardium; (b) borderline-myocarditis with low-grade focal lymphocytic infiltration; (c) acute lymphocytic myocarditis with focal cell infiltrates and necrosis of myocytes; (d) giant cell myocarditis with focal cell infiltrates and necrosis (N) of myocytes; (e) mild post-infectious interstitial fibrosis; (f) severe postinflammatory dilated cardiomyopathy with hypertrophy of the cardiomyocytes and pronounced fibrosis/scarring. Magnification x200.
are often associated with eosinophilic myocarditis (Table I) [20]. Eosinophils are also observed in myocardial inflammatory processes that are associated with Churg–Strauss vasculitis or hypereosinophilic syndromes, vaccination for several diseases or are caused by helminthic and parasitic infections (Table I).

Conclusion

Myocarditis most commonly results from an external inflammatory trigger, such as viruses or drugs, inducing a host immune response, which may range from a minimally transient response to fulminant overwhelming inflammation. Lymphocytic myocarditis is the most common form of myocarditis reported in the USA and western Europe, and virus infections are considered the most common cause of this acquired inflammatory heart disease. Severe myocarditis will lead to myocardial damage from the presence of inflammatory cell infiltrate and cytokine activation, with some contribution directly from virus-mediated cell death. These processes can severely depress cardiac function. Viruses and other acute infectious agents are usually cleared from the host by the immune system in 1–4 weeks; however, in some instances, the infectious agent genome can persist in the host myocardium for months or years, constituting a nidus for chronic inflammatory response, and a known risk factor for a worse prognosis.

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REFERENCES