Chapter 10

Infective Cardiomyopathy

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Additional information is available at the end of the chapter

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Abstract

Both the infectious agent and development of inflammatory response to infection can lead to irreversible myocardial injury, which affects the outcome of short- and long-term prognosis. In the case of the rapid elimination of the infectious agent and rapid withholding of inflammatory process, changes in myocardium are small. If the immune response does not lead to complete elimination of infectious agent or inflammation progresses after removing the virus, chronic myocardial damage may develop. Persistence of the virus in myocardium, postinfectious immune reaction, autoimmunity, and primary cardiac damage may result in the development of progressive ventricular dysfunction, development of cardiac arrhythmias, and exacerbation of symptom. Because of the long-term consequences, it is important to diagnose infective cardiomyopathy (IC) quickly and start appropriate treatment. However, IC is still a diagnostic challenge. Infective cardiomyopathy is often underdiagnosed because of a wide spectrum of factors causing IC—infectious, toxic, immunologic, and various clinical manifestation. The processes responsible for the development of IC take place at the cellular level, which is why it is important to make the diagnosis not only based on clinical symptoms and imaging but also to confirm it with the use of histological, immunohistochemical, and molecular studies. Progress in the diagnosis and understanding of the pathomechanisms responsible for the development of IC contributed to the use of new therapeutic options. Immunosuppresive and immunomodulative treatment is still of limited use. However, in some cases of viral IC, targeted antiviral treatment can be added to the standard heart failure therapy resulting in improvement of the prognosis.

Keywords: myocarditis, infective heart disease, cardiomyoapthy

1. Introduction

Infective cardiomyopathy (IC) is a disease in which structural or/and functional heart disorders are observed as a result of present or past infection caused by various infectious agents. In the course of infective cardiomyopathy heart chambers' dilatation, heart walls' hypertrophy or restriction may occur. A relation between infection and chronic heart disease was suggested as early as 1806, when Corvisart described a cardiac inflammatory disorder that could result in progressive abnormalities of cardiac function after all the evidence of the infective agent had disappeared [1]. Because of a variety of symptoms, diagnosis of IC can be difficult [2]. Usually, the suspicion of IC is based on clinical presentation and results of noninvasive diagnostic imaging, e.g., cardiac magnetic resonance (CMR) [3]. Although endomyocardial biopsy (EMB), which can confirm myocarditis, is the gold standard in making a diagnosis, it is not often performed because of its still low availability and invasiveness. However, the interest in this method is increasing lately [2]. Although more is known about the pathophysiology of the disease, many questions remain unanswered. There are many controversions about the treatment of patients with IC, especially the most common form—viral myocarditis [3].

2. Etiology

Infective cardiomyopathy may be caused by many etiological factors including viruses, bacteria, rickettsiae, fungi, protozoa, and parasites. However, the spectrum of pathogens has changed over the decades and also varies geographically as, for example, *Trypanosoma cruzi* [4]. Moreover, it can result from noninfectious agents, such as allergic agents, autoimmunity, toxins, and drugs [5]. Etiological factors that could cause IC are presented in **Table 1**.

The most popular infective agents	
Viruses	RNA viruses: Coxsackieviruses A and B, Echoviruses, Polioviruses, Influenza A and B viruses, Respiratory Syncytial virus, Mumps virus, Measles virus, Rubella virus, Hepatitis C virus, Dengue virus, Yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, Rabies virus, Human immunodeficiency virus-1 DNA viruses: Adenoviruses, Parvovirus B19, Cytomegalovirus, Human herpesvirus-6, Epstein-Barrvirus, Varicella-zoster virus, Herpes Simplex virus, Variola virus, Vaccinia virus
Bacteria	Staphylococcus, Streptococcus, Pneumococcus, Meningococcus, Gonococcus, Salmonella, Corynebacterium diphtheria, Haemophilus influenzae, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Brucella
Spirochete	Borrelia, Leptospira
Fungi	Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormyces, Nocardia, Sporothrix
Protozoa	*Trypanosoma cruzi*, *Toxoplasma gondii*, Entamoeba, Leishmania
Parasites	*Trichella spiralis*, *Echinococcus granulosus*, *Taenia solium*
Rickettsiae	*Coxiella burnetti*, *R. rickettsii*, *R. tsutsugamuschi*

Source: Modified based on Ref. [2].

Table 1. Etiological factors of IC.

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3. Diagnostic criteria for myocarditis

The common feature of the diseases that are called "infective heart disease" is myocarditis. Changes in myocarditis affect cardiomyocytes, interstitial tissue, vessels, and sometimes also the pericardium. Recent prospective postmortem data have implicated myocarditis in sudden cardiac death of young adults at rates of 8.6–12% [6, 7]. Furthermore, it has been identified as a cause of dilated cardiomyopathy in 9% of the cases in a large prospective series [8]. The diagnosis of myocarditis is based on histological, immunohistochemical, and immunological criteria [4].

3.1. Histological criteria—Dallas criteria

The Dallas criteria were proposed in 1986 and provided a histopathological categorization by which the diagnosis of myocarditis could be established (**Figure 1A** and **B**). Dallas criteria (acute) myocarditis requires an inflammatory infiltrate and necrosis or damage of adjacent muscle cells not characteristic of an ischemic event. Borderline myocarditis requires a less intense inflammatory infiltrate and no light microscopic evidence of myocyte destruction [8]. The histological diagnosis of myocarditis includes different forms, classified according to the type of inflammatory cell infiltrate: lymphocytic, eosinophilic, polymorphic, giant cell myocarditis, and cardiac sarcoidosis. The distribution and diffusion of the cellular infiltrate can be focal, confluent or diffuse, and mild, moderate or severe.

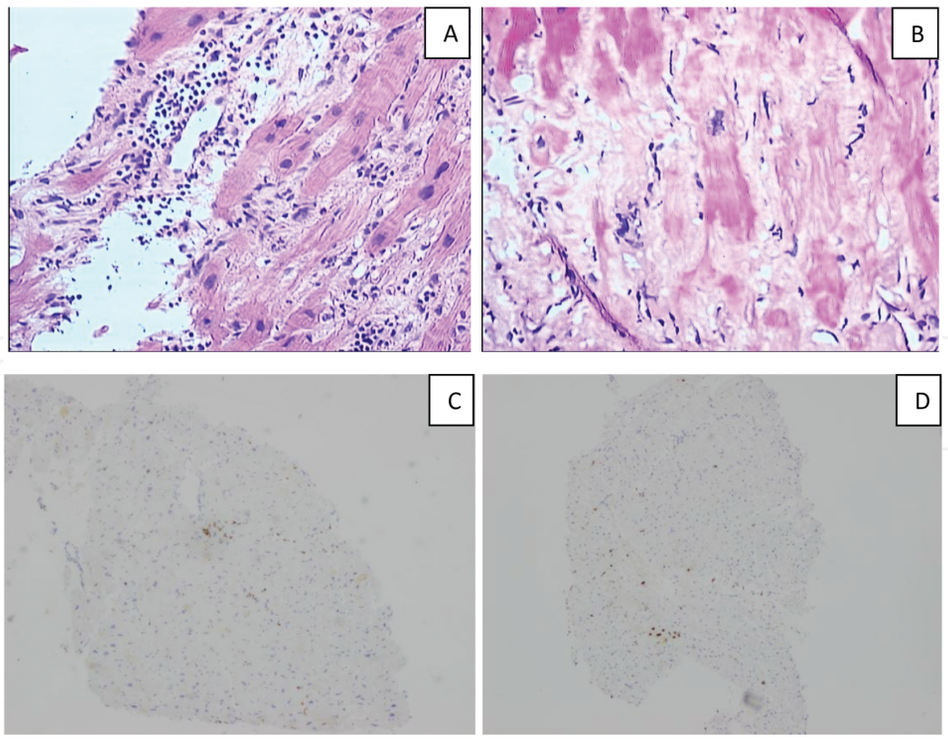

Figure 1. H&E staining, presenting numerous leucocytes (A) and myocyte damage (B). Immunohistochemical staining of leucocytes (C) and CD 3 lymphocytes (D).

3.2. Immunohistochemical criteria

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 (**Figure 1C** and **D**). Thus, immunohistochemistry 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, CD68 for activated macrophages, and human leukocyte antigen to assess HLA class II cells. With the use of these immunohistological methods, the number of EMB revealing myocarditis markedly increased. 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 the inflammatory infiltration defined as: ≥14 leukocytes/mm^2 (including ≥7 cells/mm^2 CD3 + and <4 monocytes/mm^2) [2].

Histological assessment and immunohistochemical analysis of biopsy allow the determination of the presence of inflammation in the heart. In order to determine the etiology, many frequent further studies, including polymerase chain reaction (PCR), should be performed.

4. Viral infection

Viral infections are considered to be the main cause of myocarditis in Europe and in USA [9]. It is characterized by myocardial infiltrate with lymphocytes as the predominant inflammatory cell (Lymphocytic (viral) myocarditis).

With the use of molecular techniques, EMB detection of viruses is possible in up to 67% of idiopathic left ventricular dysfunction [10]. In the past, enteroviruses (especially Coxsackie B3 and B4 viruses) were assigned to be the most common cause of IC; currently, the most common viral etiologic agents are parvovirus B19 (PVB19), human herpes virus 6 (HHV 6), and cytomegalovirus (CMV) [5, 11]. It is still not known to what extent the presence of PVB19 and HHV 6 genome detected in the myocardium affects the development of inflammation. The following forms of viral heart diseases are currently distinguished based on histopathological, genetic examinations, and results of echocardiography [12] (**Table 2**):

The form of heart disease caused by viruses	Dallas and immunohistochemical criteria	The presence of viral genome	Dilatation of left ventricle
Viral myocarditis with normal ejection fraction	+	+	–
Viral inflammatory cardiomyopathy	+	+	+
Viral heart disease	–	+	+/–

Table 2. The forms of heart diseases caused by viruses based on histopathology, genetics, and echocardiography.

4.1. Parvovirus B19 (PVB19)

Parvovirus B19 is the most common cause of viral cardiomyopathy, both in the presence or without inflammation. The presence of PVB19 has been observed significantly more often in patients with an ejection fraction (EF) <45% as compared to those of EF >45% [13]. The incidence of PVB19 DNA in patients with IC ranges from 11 to 56% according to various sources [14, 15]. The presence of PVB19 is associated with a gradual deterioration of EF, and the elimination of PVB19 from the myocardium resulted in significant improvement of ventricular function [16].

4.2. Human hepresvirus 6 (HHV 6)

The genome of HHV 6, beside PVB19, is now one of the most frequently detected pathogens during EMB [11]. Its presence has been found in 11–18% of the EMB samples [10, 15]. What is important, HHV6 can activate infections caused by other viruses such Epstein-Barr virus (EBV) and PVB19 [17]. Both HHV 6, as well as PVB19, may remain in the infected cells for a lifetime. Therefore, such a high proportion of the genome of the virus among patients with IC can be associated with the previous infection [16, 18].

4.3. Enterovirus

Presently, in patients with IC, enteroviral etiology is less frequently observed. According to various sources, enteroviral RNA is found in from 3 to 53% of the patients with IC. The majority of data is related to Coxsackievirus B3 [16]. It is important that, in contrast to PVB19 and HHV 6, up to 50% of the patients with IC, spontaneous elimination of the enteroviral genome was observed, with improvement of EF [11].

4.4. Adenovirus

Currently, adenovirus genome is less often detected during EMB, and it is present in <2% of the biopsies [19]. Patients with adenovirusal IC often present only mild clinical symptoms, and the results of biopsies analyzed according to the Dallas criteria show mild myocarditis or borderline fulfill these criteria. Therefore, adenoviral IC may have been underestimated for many years [20].

4.5. Cytomegalovirus (CMV)

Currently, CMV DNA is rarely detected during EMB performed in patients with myocardial dysfunction, and the incidence is <3%; according to some sources, it is even <1% [10, 19]. However, there are reports that the presence of CMV in immunocompetent patients is associated with the occurrence of severe IC [21].

4.6. Influenza virus

The influenza virus may also be responsible for the development of IC [20, 22, 23], and its genome is detected in <1% of the patients with IC [16]. Infectious cardiomyopathy caused by

influenza A virus may result in the development of heart failure, leading to patient's death or myocardial fibrosis with conduction defects [24]. The relationship between pandemic influenza virus H1N1 and IC is studied carefully. There are cases of acute IC observed mainly among young patients, which are associated with this pandemia [25].

4.7. The human immunodeficiency virus (HIV)

HIV infection may also cause myocarditis [26]. In a postmortem study of HIV-infected patients, myocarditis was established by histopathological criteria in more than 60% of the cases. However, most of these patients have discrete and unspecific abnormalities on the echocardiogram. In general, patients with advanced forms of HIV infection are subject to a high risk of developing overt myocarditis. HIV-related myocarditis is associated with a poor prognosis, especially in patients with low CD4+ counts (<400 cells/mm^3). These high-risk patients may develop severe left ventricular dysfunction, which could progress to advanced forms of dilated cardiomyopathy [27]. Nevertheless, it is still discussed, whether the virus, the medical treatment, or the coinfections are responsible for the development of IC in patients infected with HIV [27]. It is known that the IC related to HIV infection is characterized by a significantly worse prognosis than other lymphocytic IC [28].

4.8. Hepatitis C virus (HCV)

Hepatitis C virus is also considered to be the cause of IC [29]. HCV-associated cardiomyopathy can develop in genetically susceptible patients infected with HCV in whom viral, immunologic, and apotoptic mechanisms may lead to myocardial damage [30]. Hepatitis C virus not only causes myocarditis but also involved in the development of dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. Frequency of HCV genomes in cardiomyopathies varies in different regions or in different populations. Major histocompatibility complex class II (MHC class II) genes may be important in the susceptibility to HCV infection and may play a role in the development of different types of cardiomyopathies. It has been suggested that interferon (IFN) treatment can be useful among these patients [31].

4.9. Clinical presentation

Infectious cardiomyopathy can be completely asymptomatic [32]. The most common symptoms in patients with IC are shortness of breath, chest pain, and palpitations [33]. Often cardiac manifestation of IC is preceded by flu-like symptoms, infection of upper respiratory tract, or gastrointestinal tract. Fatigue, shortness of breath, palpitations, and atypical chest pain may occur a few days or weeks later [34]. Infectious cardiomyopathy can result in development of fulminant heart failure [27]. Since some of the symptoms may resemble acute coronary syndrome (ACS), it is important to exclude coronary artery disease (CAD) and other diseases of the cardiovascular system [2]. In some cases, the only abnormality may be nonspecific ECG changes [27]. In some cases, laboratory examinations can reveal increased troponin I, troponin T, and CK-MB, suggesting myocardial injury [35]. There are four main clinical presentations of IC (**Table 3**):

1. Acute coronary syndrome-like
2. New onset or worsening heart failure in the absence of CAD and known causes of heart failure
3. Chronic heart failure in the absence of CAD and known causes of heart failure
4. "Life-threatening condition," in the absence of CAD and known causes of heart failure comprising

Clinical presentation of patients with inflammatory heart disease
1. Acute coronary syndrome-like:
a. Acute chest pain frequently presents after respiratory or gastrointestinal infection, associated with severe or recurrent symptoms in the absence of angiographic evidence of coronary artery disease (CAD)
b. ST/T wave changes: ST-segment elevation or depression or T-wave inversion
c. With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR
d. With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months
2. New onset or worsening heart failure in the absence of CAD and known causes of heart failure
a. New onset or progressive heart failure over 2 weeks to 3 months
b. Impaired systolic LV and/or RV function, with or without dilated LV and/or RV on echocardiography or CMR
c. Symptoms possibly started after a respiratory or a gastrointestinal infection, or in the peripartum period
d. Nonspecific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block
3. Chronic heart failure in the absence of CAD and known causes of heart failure (see Point 2 above)
a. Heart failure symptoms (with recurrent exacerbations) of >3 months duration
b. Fatigue, palpitation, dyspnoea, atypical chest pain, and arrhythmia in ambulant patient
c. Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of dilated cardiomyopathy or nonischemic cardiomyopathy
d. Nonspecific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block
4. Life-threatening condition', in the absence of CAD and known causes of heart failure comprising:
a. Life-threatening arrhythmias and aborted sudden death
b. Cardiogenic shock
c. Severely impaired LV function

Source: Based on Ref. [2].

Table 3. Clinical presentation of patients with IC.

4.10. Clinicopathological classification

Myocarditis is classified based on clinical presentation, function of left ventricle, Dallas, and immunohistochemical criteria on the following:

1. Fulminant myocarditis: a presentation with acute illness following a distinct viral syndrome. Histological study reveals multiple foci of active myocarditis. Clinical presentation consists of severe cardiovascular compromise and ventricular dysfunction. This subgroup typically either resolves spontaneously or results in death. Fulminant myocarditis in most of the cases is associated with giant cell or eosinophilic myocarditis.
2. Acute myocarditis: a presentation with insidious onset of illness and evidence of established ventricular dysfunction. This subgroup may progress to dilated cardiomyopathy.
3. Chronic active myocarditis: a presentation with insidious onset of illness with clinical and histological relapses with development of left ventricular dysfunction and associated chronic recurrent inflammatory changes.
4. Chronic persistent myocarditis: a presentation with insidious onset of illness characterized by a persistent histological infiltrate frequently with foci of myocyte necrosis. Clinically, no ventricular dysfunction is present despite other cardiovascular symptoms (such as palpitations or chest pain).

4.11. Diagnostics

4.11.1. Electrocardiography

Infectious cardiomyopathy is often accompanied by nonspecific ECG abnormalities (**Table 4**). The spectrum changes to include ST-segment elevation in multiple leads, generally concave, rarely of another shape. The occurrence of atrioventricular block with a mild enlargement of the left ventricle may suggest, e.g., IC in the course of Lyme disease, sarcoidosis, or multicellular myocarditis [2]. Infectious cardiomyopathy may also result in "idiopathic" atrial or ventricular arrhythmias and reduction of PQ-segment [36, 37]. The sensitivity of the ECG is determined at 47%, but the specificity remains unknown [38]. It is recommended to perform standard 12-lead ECG in patients with suspected IC [2].

4.11.2. Echocardiography

Abnormalities revealed by echocardiography are not specific for IC. However, the use of this method allows assessing both size of heart chambers and systolic and diastolic function of the heart in patients with IC. This modality can be also useful to exclude other causes of heart failure, such as valvular heart disease or other forms of cardiomyopathy (hypertrophic cardiomyopathy and restrictive cardiomyopathy). Performing echocardiography plays especially important role in the assessment of the heart before EMB—to exclude pericardial effusion and blood clots in the cavities of the heart, which are present in 25% of the patients [39]. Moreover, evaluation of echocardiographic parameters has a prognostic significance. Patients with fulminant IC often have normal heart chamber dimensions but increased

intraventricular septum thickness due to myocardial edema, while in patients with acute IC dilatation of left ventricle and normal wall thickness can be observed [3, 40].

Diagnostic criteria	
1.	**ECG/Holter/stress test features** Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST or non-ST elevation, T-wave inversion), sinus arrest, ventricular tachycardia or fibrillation ora systole, atriafl fibrillation, reduced R-wave height, intraventricular conduction delay (widened QRS complex), abnormal Q-waves, low voltage, frequent premature beats, supraventricular tachycardia
2.	**Myocardiocytolysis markers** Elevated TnT/TnI
3.	**Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)** new, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion nor global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
4.	**Tissue characterization by CMR** Edema and/or LGE of classical myocarditic pattern

Source: Based on Ref. [2].

Table 4. Diagnostic criteria for clinically suspected IC.

4.11.3. Cardiac magnetic resonance

The use of CMR, with the assessment of early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE), is helpful in making the diagnosis of IC. In T1-weighted imaging with the assessment of the EGE, hyperintense areas show myocardium with a good blood supply, whereas the assessment of the LGE in T1-weighted imaging allows to visualize the irreversible myocardial injury resulting from the replacement of myocardial cells by fibrous tissue. Scarring and fibrosis delineated with the use of LGE-imaging are hyperechoic in contrast to normal myocardial cells. Scarring that is present in IC is located intramuscularly (typically in chronic IC) or subepicardially (typically in acute IC) [41, 42]. Location of changes in CMR enables to distinguish postinfarction scars that occur subendocardially or include the entire myocardial wall from the scars arising in the course of IC. Moreover, T2-weighted imaging reveals swelling of the myocardium, which is visible as a hyperechogenic area. Swelling in IC can be both global and regional. It reflects the reversible myocardial damage and can be present even in the absence of LGE hyperintense regions [43–45]. Cardiac magnetic resonance should be performed before EMB in hemodynamically stable patients, however, in life-threatening conditions, in which urgent EMB is necessary, it is not recommended to perform CMR [2, 46, 47].

4.11.4. Endomyocardial biopsy

Endomyocardial biopsy plays an important role in the diagnosis of IC. Nevertheless, in many clinics, it is performed only in the minority of cases with a suspicion of IC or it is not performed at all because of the lack of technical possibilities and experience. However, it is important to perform EMB in every patient with suspected IC, as it is considered to be a gold standard in making the diagnosis of IC [2, 3]. In the absence of feasibility of performing EMB, patients should be transferred to a reference center [48]. According to Schultheiss, EMB should be performed in every case of suspected IC [18, 49]. This method indicates the etiology and shows type of inflammatory infiltration, which may have therapeutic implications. According to Dallas criteria, making the diagnosis of acute IC is possible based on the presence of both lymphocyte infiltration and necrosis of cardiomyocytes, while borderline IC is defined as the presence of lympocyte infiltration and lack of cardiomyocytes necrosis [48]. Together with molecular, histological, and immunohistochemical examinations, EMB allows to start antiviral treatment or immunosuppression safely. Performing EMB has the highest level of recommendation in life-threatening IC [46]. Endomyocardial biopsy should be performed early in the course of a disease and at least 8–10 specimens should be taken, each 1–2 mm in size. Samples should be examined histologically, by immunohistochemistry and for the presence of viral genome with the use of PCR (to exclude systemic infection, it is recommended to perform viral PCR in peripheral blood at the same time). If it is necessary, EMB should be repeated to monitor the effectiveness of therapy or when sampling error is suspected [2].

When ≥1 clinical presentation and ≥1 diagnostic criteria are fulfilled, coronary angiography and EMB are recommended [2].

Infectious cardiomyopathy is clinically suspected if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories are fulfilled, in the absence of:

1. angiographically detectable coronary artery disease (coronary stenosis ≥50%);
2. known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g., valve disease, congenital heart disease, and hyperthyroidism). Suspicion is higher with higher number of fulfilled criteria. If the patient is asymptomatic, ≥2 diagnostic criteria should be met [2].

4.12. Treatment

In the course of IC, cardiomyocytes can be damaged by direct action of the virus, antiviral immune response, or autoimmune response. As the cardiomyocytes are not able to regenerate, improvement of myocardial function mainly depends on the tissue not affected by inflammation. Response to treatment depends on the cause of IC, and the severity of irreversible changes presents at the moment of initiation of treatment [50].

Regardless of the cause, IC therapy is based on optimal treatment of heart failure, consisting of the use of angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers and/or β-adrenergic receptors' blockers [50–52]. There are well-known studies that confirm the efficacy of captopril and candesartan in the treatment of IC [53, 54]. Moreover, it is

recommended to reduce physical activity during the acute phase of IC and for at least 6 months after the onset of the disease [2].

4.12.1. Antiviral treatment

Elimination of viruses from cardiomyocytes results in decrease in the symptoms reported by patients. It also affects the heart chambers' size, improvement of left ventricle EF, and reduction of long-term mortality [55]. Targeted antiviral therapy can result in total elimination of the virus genome or, even if the total elimination is not possible, it can reduce the patient's complaints. Nevertheless, starting antiviral therapy is useful only early in the course of a disease, when irreversible changes in the myocardium are not present yet [18]. In IC caused by HHV6, valacyclovir, and ganciclovir can be used [2, 17]. The use of interferon β (IFN-β) enables to eliminate adenoviruses and enteroviruses from cardiomyocytes, improving also heart efficiency. After treatment with IFN-β, increase in EF, decrease in left ventricle, reduction in heart failure symptoms, and smaller inflammatory infiltration were observed [55]. Interferon β can also be used in IC caused by PVB19—it can reduce the symptoms and endothelium dysfunction, but it has only little effect on the elimination of the virus [18]. Mechanism of beneficial clinical effects of IFN-β is not known, but IFN-β inhibits reactivation of PVB19 and improves the viability of endothelial cells [56]. Similarly, in IC caused by HHV6, treatment with IFN-β or ganciclovir does not eliminate virus from the myocardial tissue, probably because of viral genome integration with host genome. However, in patients with HHV6, IC ganciclovir reduces clinical symptoms [57].

4.12.2. Immunosuppression

Immunosuppression with the use of steroids, combination of steroids and azathioprine or azathioprine, cyclosporine A, and steroids is safe and efficient in IC. So far there is no data about the use of other Immunosuppresive drugs in IC treatment [2]. It is important to perform EMB before initiation of immunosuppression to exclude viral etiology of IC [50] because only patients with autoimmune IC benefit from immunosuppression [58–60]. Therefore, immunosuppression should be considered in patients with autoimmune IC, including giant-cell IC, sarcoidosis, IC in the course of "noncardiac" autoimmune diseases, who do not have contraindications for immunosuppressive therapy. The use of steroids is indicated in sarcoidosis with ventricle dysfunction and/or arrhythmia and in some cases of noninfectious eozynophilic IC or toxic IC with concomitant heart failure and/or arrhythmia. When there are no contraindications, immunosuppression can be also considered in noninfectious lymphocytic IC resistant to standard therapy [2].

4.12.3. High-dose intravenous immunoglobulin

No consensus exists on the benefits of high-dose intravenous immunoglobulin (IVIG) in the treatment of IC. Although there are reports confirming the improvement of left ventricular function and increase in one-year survival after application of IVIG [61], finally, it appears that this therapy has no positive effect on progression of IC [62, 63].

4.12.4. Immunoabsorption

The aim of immunoabsorption (IA) is elimination of antibodies against cardiac proteins [64]. There are some studies that confirm the efficacy of IA in dilated cardiomyopathy [65, 66]. However, multicenter, randomized studies are needed to recommend the use of IA in a standard IC therapy.

5. Other heart infections

5.1. Bacterial infections

Bacterial myocarditis with no coexisting endocarditis occurs extremely rarely. Usually, it results from massive bacteremia. *Staphylococcus aureus* is a main etiological factor of bacterial myocarditis. Nevertheless, cardiac involvement in the course of streptococcal (*Streptococcus pyogenes*, *Streptococcus viridans*, and *Streptococcus pneumoniae*) infection has also been reported [67]. Moreover, myocarditis can be the result of meningococcal disease or can be associated with *Salmonella*, *Listeria monocytogens*, or *Corynebacterium diphtheria* infection [68–71]. Bacteremia, neutropenia, myocardial infarction, osteomyelitis, and recent surgical procedures are considered to be main risk factors of bacterial myocarditis. Clinical manifestation is dominated by sepsis and heart failure symptoms. To confirm the diagnosis, EMB should be performed, revealing active myocarditis with evidence of bacterial invasion or positive tissue cultures [71]. Standard treatment consists of aggressive targeted antibiotic or antitoxin therapy and appropriate hemodynamic support, in conjunction with the treatment of arrhythmias or mechanical complications [67, 71].

5.1.1. Mycobacterium tuberculosis

Myocarditis is a very rare manifestation of Mycobacterium tuberculosis infection. There are three types of myocardial tuberculosis: nodular tubercles of the myocardium, miliary tubercles of the myocardium, and diffuse infiltrative type associated with tuberculous pericarditis. Cardiac tissue can be infected by hematogenous spread, by retrograde lymphatic spread from mediastinal lymph nodes, or directly from the pericardium. In patients with strong suspicion of cardiac tuberculosis, EMB should be performed to confirm the diagnosis. Clinical presentation is nonspecific and varies from ventricular fibrillation, long QT syndrome, congestive heart failure, and DCM to sudden cardiac arrest. However, a large number of patients are completely asymptomatic. Anti-tuberculosis therapy is usually effective; nevertheless, it does not reduce the risk of sudden cardiac death [72].

5.1.2. Tropheryma whipplei

Whipple's disease is a rare bacterial infection, which usually affects the intestinal tract, but it can also involve other organs. Cardiac manifestation of Whipple's disease occurs in 35–60% of affected patients. Infectious endocarditis with negative blood cultures develops most commonly. Whipple's disease may also present as adhesive pericarditis and myocardial fibrosis.

Lymphocytic myocarditis is unusual [73]. Cardiac involvement can clinically present as congestive heart failure, conduction disturbances, arrhythmias, or even sudden cardiac death. It is suggested that chronic damage of heart tissue is the cause of death in most patients with end-stage disease [74]. It is difficult to confirm the diagnosis due to lack of culture and serodiagnostic methods. Currently, detection of *T. whipplei* by PCR is a method of choice to establish the diagnosis. Treatment of Whipple's disease remains empirical; it is suggested to use trimethoprim-sulfamethoxazole for at least 1 year, or, alternatively, an initial parenteral therapy with penicillin and streptomycin for 2 weeks followed by trimethoprim-sulfamethoxazole [73].

5.2. Spirochetes infection

5.2.1. Borrelia burgdorferi

Lyme disease (LD) that is caused by *B. burgdorferi* mostly affects skin, heart, nervous system, and joints [75]. The most common cardiac manifestation of LD is conduction and rhythm disturbances, most frequent of which is atrioventricular (AV) block [76]. However, LD can also result in myocarditis and new-onset of DCM, especially in the highly endemic area for LD [75, 77]. Serological diagnosis in patients with cardiac LD may be difficult, as IgM and IgG antibodies against *B. burgdorferi* are frequently negative at first; a measurable level of antibodies develops in the course of illness [75, 78]. Therefore, EMB can be extremely useful in making the diagnosis of DCM caused by *B. burgdorferi* [79]. Early treatment with antibiotic therapy (intravenous infusion of ceftriaxone) is effective and leads to significant improvement of left ventricle ejection fraction and reduction of heart failure symptoms [75, 79].

5.3. Fungal infection

Fungal myocarditis mostly develops in immunodeficient patients. Therefore, it can be often clinically latent or masked by neurological or respiratory symptoms [80].

5.3.1. Aspergillus

Cardiac aspergillosis occurs mostly in patients with immunodeficiency or immunosuppression such as cancer, hematological conditions, or organ transplantation. Cardiac involvement occurs as a result of disseminated *Aspergillus* infection. It is associated with high mortality rate because of late diagnosis and lack of effective therapy [81].

5.3.2. Blastomycosis

Cardiac blastomycosis can develop by an extension from pericardial blastomycosis, by a direct involvement of heart tissue, or by a lymphatic spread from mediastinal lymph nodes. It often leads to congestive heart failure, with heart chambers dilatation and little hypertrophy. The course of cardiac blastomycosis has many common features with cardiac tuberculosis [82].

5.3.3. Candida

Candida is not pathogenic among immunocompetent hosts, but it can cause severe mucosal or systemic infections in immunocompromised patients [83]. *Candida* invasion of the heart significantly complicates the clinical course of candidiasis and aggravates the patients' condition and should be suspected when arrhythmia, conduction disturbance, or other QRS changes occur in patients with systemic candidiasis [84].

5.4. Protozoan infections

5.4.1. Trypanosoma cruzi

Chagas disease is caused by infection with *Trypanosoma cruzi* (*T. cruzi*), which is transmitted by blood-sucking insects and small mammals. The disease is common in the southwestern part of United States, Mexico, Central, and South America [85]. Contact of skin lesions, mucosal surfaces, or the conjunctiva with parasites present in the feces of the insect leads to infection with *T. cruzi*. In nonendemic countries, transmission is also possible with blood transfusion, organ transplantation, and vertical way [86].

In the course of Chagas disease, two phases are described: an acute and a chronic phase [86]. Patients with acute Chagas disease may present nonspecific symptoms or may be completely asymptomatic. Moreover, acute myocarditis, pericardial effusion, and/or meningoencephalitis can develop in the course of acute infection [85]. In a majority of patients, the acute phase subsides spontaneously after 6–8 weeks [86]. In some of the infected patients, chronic Chagas disease develops with the symptoms from various organs [86]. Patients with chronic Chagas cardiomyopathy can present symptoms of heart failure, arrhythmias, thromboembolism (systemic or pulmonary), and chest pain [85]. Echocardiography may be useful in making the diagnosis of Chagas cardiomyopathy. It can reveal a specific pattern of segmental myocardial contractility disturbance, mainly localized in left ventricular apex and inferior-posterior wall [86]. Moreover, in chronic Chagas cardiomyopathy, echocardiography can show severe dilation of the heart chambers characteristic aneurysm localized in left ventricle's apex [85]. Because of high risk of thromboembolism, transesophageal echocardiography can be helpful to identify cardiac sources of emboli and make decision about anticoagulant treatment [85]. Histopathologically myocytolysis, reparative fibrosis, and lymphocytic infiltrates are seen in Chagas heart disease. Treatment of Chagas cardiac disease consists of targeted antiparasitic therapy and treatment of heart failure, arrhythmias, and thromboembolism [86]. Benznidazole is used to eliminate *T.cruzi*, and it is effective in acute phase [87]. Its efficacy in chronic Chagas cardiomyopathy is still discussed [86]. Angiotensin-converting enzyme (ACE) inhibitors and β-blockers can be useful in heart failure therapy. Because of high risk of thromboembolism in Chagas disease, oral anticoagulation should be considered with cardioembolic risk score for Chagas disease patients [86]. Moreover, pacemaker or ICD implantation may contribute to a better survival in some patients with Chagas disease [87].

5.5. Parasitic infection

5.5.1. Echinococcus

Echinococcal infection develops after consumption of *Echinococcus* eggs from the feces of infected dogs or other canids. In the majority of cases, the disease involves liver or lungs. Heart is a very rare localization of parasites' cysts. Cardiac echinococcosis can manifest as arrhythmias, myocardial infarction, cardiac tamponade, pulmonary hypertension syncope, purulent pericarditis, and sudden cardiac death. The basis of making the diagnosis is serology and echocardiography, which can visualize myocardial or pericardial hydatid cysts. Moreover, with the use of CMR or computed tomography calcification of the cysts' walls can be shown. Albendazole or mebendazole should be used in the treatment of cardiac echonococcosis [88].

6. Autoimmune heart inflammation

6.1. Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Clinical presentation varies among patients. Sarcoidosis mostly affects skin, lymph nodes, lungs, eyes, and the central nervous system. Cardiac involvement will occur in approximately 5% of the patients with sarcoidosis [89] and varies in the different geographical regions, but it is considered to be very important prognostic factor in this disease [90]. Cardiac sarcoidosis may present as acute heart failure, ventricular arrhythmia, conduction disturbances, and even sudden death. Diagnosing cardiac sarcoidosis may be difficult due to nonspecific ECG and echocardiographic findings; therefore, it is often misdiagnosed. To make the right diagnosis, the use of endomyocardial biopsy (EMB), cardiac magnetic resonance (CMR), and ^{18}F-fluorodeoxyglucose positron emission tomography may be helpful. Patients should be treated with corticosteroids, which help to control inflammatory process, prevent fibrosis, and protect from aggravation of the cardiac function [90].

6.2. Churg-Strauss syndrome (CSS)

Churg-Strauss syndrome is a rare systemic vasculitis, which affects small- and medium-sized blood vessels, characterized by eosinophil infiltration of various tissues [91]. It occurs in patients with an atopic condition, typically with a previous history of asthma or allergy disease. According to different sources, cardiac involvement is reported in 16–92% of patients with CCS [92, 93]. Cardiac changes are associated with a poor prognosis and high mortality, if not treated [94]. There are two types of cardiac involvement in CSS: vasculitis-related ischemia and eosinophilic infiltration of the myocardium. It can present as myocarditis with cardiomyopathy, pericarditis, pericardial effusion, heart failure, ventricular and supraventricular arrhythmias, and sudden cardiac death. Heart involvement is characterized by both fibrosis and an active inflammatory process. Changes visualized by CMR with LGE are mostly localized in the subendocardium [95, 96], but they can be also observed in the intramural and subepicardial

myocardium [97]. Patients with cardiac involvement are mainly antineutrophil cytoplasmic antibody (ANCA)-negative. The management of myocarditis in the course of CCS includes standard therapy for heart failure and immunosuppressive treatment with steroids [98]. Initiation of treatment allows recovery of cardiac function and reduces symptoms of heart failure.

6.3. Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is an autoimmune disease, which usually occurs in young females. Cardiac involvement is one of the most frequent manifestations. All anatomical heart structures can be affected: pericardium, myocardium, valves, coronary arteries, and the conduction system [99]. Several autoantibodies, such as anti-phospholipid antibodies (aPL), anti-SSA/Ro antibodies, and anti-endothelial cells antibodies, can contribute to heart damage in SLE. Antibodies-SSA/Ro and anti-SSB/La antigens are responsible for the development of heart conduction disorders in the neonatal lupus syndrome.

Myocarditis is uncommon, but a serious presentation of SLE can lead to cardiac dysfunction or even sudden cardiac death [100]. Early diagnosis of lupus myocarditis is important because of the likely progression to arrhythmias, conduction disturbances, dilated cardiomyopathy, and heart failure [101]. Echocardiography is a sensitive and specific technique, and it can not only reveal global hypokinesis in patients with SLE myocarditis but also visualize other cardiac manifestations of SLE, such as pericarditis or valvular lesions [102]. In patients with lupus myocarditis, CMR shows LGE; however, it cannot differentiate these changes from myocarditis of other etiology [99]. Therefore, endomyocardial biopsy is the gold standard technique in making the diagnosis [103]. Histopathological examination shows immune complexes with mononuclear cell infiltrates, perivascular inflammation or arteriopathy, and necrosis of the cardiomyocytes [99]. Early treatment with high-dose steroids is the basis of lupus myocarditis therapy. In severe cases, intravenous pulse corticosteroid should be administered. Azathioprine, cyclophosphamide, or intravenous immunoglobulines (IVIG) may be useful [103].

7. Summary

Both the infectious agent and development of inflammatory response to infection can lead to irreversible myocardial injury, which affects the outcome of short- and long-term prognosis. In the case of the rapid elimination of the infectious agent and rapid withholding of inflammatory process, changes in myocardium are small. If the immune response does not lead to complete elimination of infectious agent or inflammation progresses after removing the virus, chronic myocardial damage may develop. Persistence of the virus in myocardium, postinfectious immune reaction, autoimmunity, and primary cardiac damage may result in the development of progressive ventricular dysfunction, development of cardiac arrhythmias, and exacerbation of symptoms [18]. Because of long-term consequences, it is important to diagnose IC quickly and start appropriate treatment. However, IC is still diagnostic challenge.

Infective cardiomyopathy is often underdiagnosed because of a wide spectrum of factors causing IC—infectious, toxic, immunologic, and various clinical manifestations [3]. The processes responsible for the development of IC take place at the cellular level, which is why it is important to make the diagnosis not only based on clinical symptoms and imaging but also to confirm it with the use of histological, immunohistochemical, and molecular studies [18]. Progress in the diagnosis and understanding of the pathomechanisms responsible for the development of IC contributed to the use of new therapeutic options. Immunosuppresive and immunomodulative treatment is still of limited use [2]. However, in some cases of viral IC, targeted antiviral treatment can be added to standard heart failure therapy resulting in improvement of the prognosis [18].

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