Viral cardiomyopathy: A review of clinical status and meta-analysis of diagnosis and clinical management

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Abstract
From an aetiological standpoint, viral cardiomyopathy represents an uncommon subtype of non-inflammatory dilated cardiomyopathy. The most common aetiologic agents are enteroviruses, adenoviruses and erythroviruses. Pathogenesis depends on the causative virus. Enteroviruses and adenoviruses infect and injure the cardiomyocyte through cytopathic effect and immune-mediated damage leading to cardiac remodelling, myocarditis and ultimately cardiomyopathy. Erythroviruses infect and injure the vascular endothelial cells resulting in macrovascular dysfunction. Typical clinical presentation is heart failure, arrhythmias and chest pains. Clinical diagnosis requires the presence of electrocardiographic abnormalities, markers of myocardial necrosis or evidence of functional/structural ventricular abnormalities accompanied by at least one physical sign or clinical symptom. However, endomyocardial biopsy remains the reference standard but increased risks of complications and the need for highly experienced operators limits its widespread use. The available clinical management strategies are standard heart failure medication for the management of cardiac dysfunction and antiarrhythmic drugs for those with ventricular arrhythmias. Patients with refractory symptoms greater than six months despite optimal medical therapy and with biopsy-proven virus negative myocardium may benefit from supplementary immunosuppressive therapy. However, large-scale and long-term prospective randomized clinical trials are warranted to determine long-term benefits of immunosuppression.

Introduction
Classification systems in clinical medicine have been pivotal in facilitating the development of standardized disease nomenclature, focused disease research and the development of safe and efficacious clinical management strategies. In the case of cardiomyopathies (CM), classification has proved exceedingly complex. Underpinning this complexity is considerable phenotypic overlap and heterogeneous clinical presentations between categories and in the same category during the natural course of the disease. The World Health Organization (WHO) and the European Society of Cardiology (ESC) propose a morphofunctional classification while the American Heart Association (AHA) propose primary vs secondary classification based on myocardial and/or organ involvement [1-4]. All these classifications suffer significant overlap between individual categories. Aetiological classification is also imperfect since categories with similar genotypes may exhibit different phenotypes and pathogenic pathways and vice-versa [3]. Nevertheless, the most recent MOGES classification that incorporates morphofunctional, organ-involvement, inheritance pattern, aetiology and underlying disease underscores the importance of aetiological classification in advancing the knowledge and understanding of the pathogenesis of a disease [5,6]. This paper provides a review of available published evidence and expert consensus on virus aetiologies of CM including the role of aetiologies in the diagnosis and treatment of viral CM.

Clinical definitions
The 2006 AHA scientific statement on contemporary definitions and classification of the cardiomyopathies defines CM as “a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality” (p. 271) [2]. Dilated cardiomyopathy (DCM) in which virus forms part of the aetiologic agents, is a phenotype characterized by ventricular dilatation and depressed myocardial performance in the absence of coronary artery disease or abnormal loading conditions [3]. Thus, viral CM may be considered a sub-type of DCM defined by viral persistence in a dilated heart. When viral persistence is accompanied by myocardial inflammation, the disease may be termed inflammatory CM or viral myocarditis (VMC) with cardiomegaly. However, if there is no biopsy evidence of inflammation on a dilated heart (< 14 lymphocytes and macrophages/mm²), then the term viral CM (VCM) or viral persistence DCM should be applied [7].

Epidemiology
Viral infection of the heart is relatively rare and usually asymptomatic with spontaneous and complete resolution. However, in uncommon cases, it may lead to substantial cardiac damage, the development of VMC, VCM and congestive heart failure (HF) [7]. Usually, VMC occurs in all age groups from infants to older adults but it is prevalent in children and adults under the age of 40, with 35% of the patients aged 10-30 years old [8]. However, accurate determination of the prevalence and incidence of viral heart infection has been

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problematic due to a wide variety of viruses and several periods of epidemic, which lead to significant differences in the predominant viruses in different regions as well as in different years within the same region. In addition, the low use of virological tests has resulted in few epidemiological data on viral heart infection. However, three categories of epidemiological data provide important insights into the prevalence of viral heart infection: (a) data from autopsy or biopsy examinations; (b) data from clinical diagnosis during periods of viral epidemic; and (c) data from population-based studies.

**Data from autopsy/biopsy examination**

Available autopsy and biopsy data suggest a very low prevalence of both viral heart infection and VMC. Analysis of 377,841 cases of autopsy between 1958 and 1977 from the Japanese Pathology Society found low incidence of non-specific myocarditis (0.11%) and tuberculosis myocarditis (0.007%) [9]. In Italy, an analysis of 17,162 autopsy cases between 1965 and 1994 reported a low incidence of VMC (0.53%) [10]. The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESTCID) conducted between 1993 and 1999 investigating endomyocardial biopsies of 3,055 patients found 526 cases (17.2%) of acute or chronic VMC [11].

**Data from clinical diagnosis**

Data from clinical diagnosis of viral infection of the heart during viral epidemic periods indicate significantly higher incidence of between 5 and 10%. In 1981 during the period of influenza epidemic in China, virus antibodies were positive in 43% of 183 patients with fever, in which 13 cases were consistent with clinical diagnosis of VMC with an incidence of 7.1% [11]. Paired virus serum antibody was positive in 43% of 1,426 VMC-suspected patients between 1978 and 1986, which was similar to the year 1981, where reported cases of VMC was 28% in 526 cases (17.2%) of acute or chronic VMC [11].

**Data from population-based studies**

Population-based studies report very low incidence of viral heart infection and myocarditis. A collaborative group in nine provinces and cities in China between 1978 and 1980 investigating the incidence of VMC reported 1,709 paediatric, 136 VMC-suspected, and 90 cardiomyopathy, with VMC incidence ranging between 6.8 to 29.2 per 100,000 [4]. A review of 1,349,828 deaths in Finland between 1970 and 1998 reported an incidence of 0.47 per 1,000 deaths due to myocarditis. The incidence remained constant in the 1970s through to the 1980s rising in the 1990s [13]. In Yunnan province in China, variation in prevalence was associated with income levels and geographic locations, with an average incidence of 1.2% between 1978 and 2004 [14]. At present, the incidence of VMC in China has risen from the 10th to the 4th leading heart disease based on records of patients hospitalized with heart diseases [15].

**Aetiologic agents**

A broad spectrum of infectious agents is involved in the pathogenesis of viral CM. The spectrum varies with geographical region, patient’s age, treatment used and the presence of concomitant diseases [7]. Table 1 provides a list of the common aetiologic agents of VCM alongside their primary or main diseases. Although numerous viruses may be involved in the initial myocardial infection and subsequent development of VCM, the most commonly observed viruses in VCM patients are erythrovirus (Parvovirus B19), enteroviruses (coxackievirus) and adenoviruses [16]. However, it is almost possible to quantify the exact frequency that cardiomyotropic viral infection lead to clinically significant VMC and VCM. Such quantification would require tissue sampling from otherwise healthy individuals during a viral epidemic [7].

**Coxackievirus**

Coxackievirus is a member of the *picornaviridae* family in the enterovirus genus of viruses. They are positive-sense single-stranded RNA viruses divided into coxackievirus A (CVA) and B (CVB) species [17]. The CVA species is the major causative agent of both epidemic and sporadic cases of hand, foot and mouth disease, and herpangina (painful mouth blisters) [18-20]. In children, CVB is a unique cause of syndromes such as myopericarditis and pleurodynia (Bornholm disease). Other CVB-related diseases include infections of

| Aetiologic agents | Common diseases associated with infection |
|-------------------|------------------------------------------|
| 1. Coxsackievirus | Hand, foot and mouth disease, herpangina or pleurodynia (Bornholm disease) [17-31]. |
| 2. Parvovirus | Erythema infectiosum (fifth disease), polyarthropathy, transient aplastic crisis, pure red cell aplasia, hydrops fetalis or congenital anaemia [32-34]. |
| 3. Adenovirus | Keratoconjunctivitis, respiratory and enteric infection gastroenteritis, hepatitis, pneumonia, meningoencephalitis, cystitis, upper or lower respiratory tract infections [35-40]. |
| 4. Herpes virus | Exanthema subitum (sixth disease), encephalitis, mesial temporal lobe epilepsy and multiple sclerosis [41-48]. |
| 5. Cytomegalovirus | CMV mononucleosis or CMV-associated graft failure [50-56]. |
| 6. Varicella virus | Chicken pox, herpes zoster (shingles) [57-62]. |
| 7. Hepatitis virus | Acute/chronic hepatitis or hepatocellular carcinoma [63-70]. |
| 8. Influenza virus | Influenza [71-77]. |
| 9. Poliovirus | Poliomyelitis [78-83]. |
| 10. Mumps virus | Mumps [84-86]. |
| 11. Rubella virus | Rubella (German measles), congenital rubella syndrome [87,89]. |
| 12. Rubella virus | Measles [90-94]. |
| 13. Varicella | Smallpox [95-98]. |
| 14. Epstein-Barr | Infectious mononucleosis, epithelial and lymphocytic carcinoma [99-105]. |
| 15. Echovirus | Aseptic meningitis, encephalitis [106-110]. |
| 16. Rabies virus | Rabies [111-116]. |
| 17. Mycoplasma virus | Viral pneumonia [117-122]. |
| 18. Psittacosis virus | Atypical pneumonia (psittacosis) [123-126]. |
| 19. HIV | Acquired Immunodeficiency Virus (AIDS) [127-139]. |
| 20. Arbovirus | Encephalitis, epidemic mosquito-borne arboviruses (yellow fever virus, dengue virus, West Nile virus, chikungunya virus and Zika virus) [140-144]. |
the central nervous system, respiratory tract and vertically transmitted infections (mother-to-child/embryo) [21]. Coxsackievirus infections are also responsible for several inflammatory conditions including myocarditis, pericarditis, pancreatitis, meningitis and encephalitis [22]. Coxsackievirus is a common cause of acute MC in children or young adults (< 35 years) [23-25] and about a half of healthy individuals have detectable serum antibodies indicating prior infection [26-28]. Tests based on polymerase chain reaction (PCR) reveal positive-strand enteroviral RNA in 35% of DCM patients [29]. Analysis of a German registry data shows low incidence of enteroviral MC (3%) and enteroviral CM with or without inflammation (4% each) [7]. Necropsy analysis of enteroviral CM patients reveal pericardial effusion, cardiomegaly, and a predominant mononuclear inflammatory infiltrate accompanied by necrosis of the atrial and ventricular myocardium, and in some patients, focal myocardial necrosis mimicking myocardial infarction despite normal coronary arteries [30]. Cardiac susceptibility to viral infection is due to affinity for myocardial membrane receptors (human Coxsackie-adenovirus receptor [hCAR]) to viral particles [31].

**Parvovirus**

Parvovirus B19 (PVB19) is a member of the Parvoviridae family in the erythrovirus genus of small round, non-enveloped single-stranded RNA virus [32]. It is an autonomously replicating virus and the main site of infection is erythrocyte precursors [33]. The PVB19 virus is widespread and the clinical picture associated with its infection vary based on the immunologic and hematologic status of the infected individual. In healthy immunocompetent children, PVB19 is the aetiologic agent of erythema infectiosum (fifth disease), an innocuous rash illness. In adults, infection is occasionally associated with an acute symmetric polyarthropathy mimicking rheumatoid arthritis. Due to tropism of PVB19 to erythroid progenitor cells, infection in individuals with an underlying haemolytic disease causes transient aplastic crisis. In immunocompromised individual, persistent PVB19 infection may cause pure red cell aplasia and chronic anaemia. Infection in foetus may lead to death in utero, hydrops fetalis or congenital anaemia [32,33]. In rare cases, PVB19 infection has been associated with several syndromes including vasculitis, encephalitis, pruritis, congenital red cell aplasia, chronic bone marrow failure and Kawasaki disease [33]. Since the heart and kidney express receptors for PVB19, it could lead to myocarditis, and complications and/or rejection in liver and renal transplant patients [33]. Recently, PVB19 infection has been associated with myocarditis and viral cardiomyopathy with high mean numbers of virus copies in EMB – 2013 in inflammatory DCM compared to 57 in non-inflammatory DCM and 44 in HCM [7]. Pankuweit et al. analysis of PCR series reported up to 30% of endomyocardial biopsy (EMB) samples in patients with DCM and MC [34].

**Adenovirus**

Human adenovirus (HAdV) is a non-enveloped, double stranded DNA virus belonging to the family *Adenoviridae* in the genus *Mastadenovirus* that contains seven known species: HAdV-A to HAdV-G [35-37]. The primary sites of infection include the gastrointestinal tract, lung, urinary tract, upper respiratory tract and eye [35]. Common transmission pathways include exposure to infected individuals via inhalation of contaminated aerosolized droplets or direct conjunctival inoculation, or through faecal-oral spread such as contact with infected recreational fresh-water or tap water, airflow filters or environmental surfaces [38]. Although HAdV are prevalent in water bodies such as in rivers, coastal waters, swimming pool and drinking water, they can retain their infectious properties for several weeks in moisture free environments, and are resistance to disinfectants [38,39]. HAdV infection mainly causes keratoconjunctivitis as well as have been associated with complications such as gastroenteritis, hepatitis, myocarditis and pneumonia mostly in children (< 5 years) [36]. HAdV infection accounts for 3% to 5% of acute respiratory infections in children and < 2% in civilian adults [40]. In immunocompromised patients, infection has been associated with high morbidity and mortality [37-39]. Relative to other viral causes of CM, it is the second most frequent virus (after Coxsackievirus) found by PCR examinations in EMB of patients with viral cardiomyopathy [40]. In patients with MC and DCM, positive PCR ranges between 5% and 8% [7].

**Human herpes virus**

Human herpes virus (HHV-6) is a double stranded DNA virus belonging to *Betaherpesvirinae* subfamily in the genus *Roseolovirus* with two closely related yet distinct variants: HHV-6A and HHV-6B, which are two of the eight herpes viruses (HHV1-8) in which the human body is the primary host [41-43]. Over 95% of the individuals older than two years are seropositive for HHV-6A and/or HHV-6B. [41,41]. HHV-6 exhibits a wide cell tropism in vivo (lymph nodes, macrophages and monocytes, kidney tubule endothelial cells, salivary glands and CNS tissues, and induces a lifelong latent infection [41,42]. In immunocompromised individuals (by either natural means or pharmacologic interventions), HHV-6 may cause serious disease including enanthema subitum (sixth disease: a benign disease of infancy) as a primary infection while further virus reactivation can induce severe encephalitis mostly in hematopoietic stem cell transplant patients [42-44]. Due to high tropism for CNS cells, HHV-6 has been associated with a diverse array of neurologic diseases including seizures, encephalitis, mesial temporal lobe epilepsy and multiple sclerosis [43]. Immunocompromised patients such as those undergoing renal/bone marrow transplant are at a greater risk for post-transplant disease or complications [41]. HHV-6 is a common cause of viral MC (10.5%) and viral CM (21.6%) [45,46]. Although the exact pathogenic role of HHV-6 is still a matter of research, viral persistence or presence may be responsible for fatal MC in children aged between 4 and 24 months or the progression to DCM in infected individuals [47-49].

**Cytomegalovirus**

Human cytomegalovirus (CMV) is an enveloped double-stranded DNA virus belonging to the viral family *Herpesviridae* of the genus *Cytomegalovirus* [50,51]. The CMV can infect any organ but more commonly occur in the blood, brain, colon, heart, kidney, lung and stomach [52]. Primary infection is rare in individuals aged younger than 35 years but prevalent in immunosuppressed individuals [53-55]. Its main transmission route is contact with the mucous membrane or parenterally via blood components containing cells or via stem cell or organ transplant [50]. Other important transmission routes include peri-natal and post-natal mother-to-foetus through transplacental, cervical or vaginal secretions and breast milk, and sexual transmission via cervical secretion and semen or via the saliva [51]. Immunocompromised patients such as those receiving organ transplants or treatment for HIV/AIDS or cancer are at increased risk of serious complications [50]. Mostly, CMV infection is associated CMV mononucleosis, as well as a host of end-organ diseases (pneumonia, gastrointestinal disease, hepatitis disease, CNS disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis splenomegaly and colitis) and CMV-associated graft failure [50,51]. Cardiac involvement in CMV infection is rare. In a German hospital register, CMV-associated MC was found in <3% of the respective patient cohort [7]. Reported
prevalence of CMV in MC and DCM patients is 3% and 0.8% [45,46]. Cardiac infection in adults present as asymptomatic and transient electrocardiographic abnormalities. Symptomatic cardiac involvement is rare but in some immunosuppressed individuals, haemorrhagic pericardial effusion or MC with LV dysfunction, and attendant congestive HF may manifest [54-56].

**Varicella virus**

Varicella virus (also known as human herpes virus-3) is a ubiquitous enveloped, linear double stranded DNA virus belonging to the human alpha-herpesvirus family of viruses [57,58]. The virus only naturally infects humans with no animal reservoir. Its main infection targets are T lymphocytes, epithelial cells and ganglia [58]. It spreads by airborne route and its transmission is through the respiratory tract [58,59]. Primary varicella infection causes chicken pox, a common childhood illness associated with fever and general pruritic vesicular rash. Varicella virus establishes latency in the cells of the dorsal root ganglia (even for decades) after the primary infection. It is a less common infection in tropical areas, but in temperate climates, children acquire chicken pox between the fifth and tenth years of life. Second episode of chicken pox is very rare. Reactivation of varicella in the host results in shingles (or herpes zoster), a localized, painful vesicular rash involving one or adjacent dermatomes, whose incidence increases with age or immunosuppression [57-59]. Shingles may be complicated by chronic pain (postherpetic neuralgia) or the presence of other serious neurological and ocular disorders such as meningoencephalitis, myelitis, cranial nerve palsies, vasculopathy, keratitis and retinopathy [58]. MC is an uncommon but a serious complication of varicella infection but unsuspected MC is a common finding in fatal varicella infection [60]. Histological findings may reveal characteristics intranuclear inclusion bodies with myocardial cells accompanied with interstitial oedema, cellular infiltrates and myonecrosis [61]. Varicella infection causing viral MC can progress rapidly to DCM as well as result in life-threatening arrhythmias [60-62] (Figure 1).

**Figure 1. Pathogenesis of viral cardiomyopathy**

Viral infection of the cardiomyocyte result in direct cytopathic effect leading to cell damage or death. Innate immune response eliminates viral particles and infected cells during the initial virus entry and replication (acute myocarditis). Fulminant myocarditis is rare resulting from disturbances in control mechanism of inflammation. In immunosuppressed patients, ineffective or delayed innate immune response, weak cytotoxic T-lymphocyte response or insufficient antibody production allows viral diffusion within the heart. Chronic viral presence result in constant but still ineffective infiltration of immune cells leading to chronic inflammation. This process accompanied by loss of damaged contractile tissue and the appearance of fibrosis may result in viral cardiomyopathy – a form of dilated cardiomyopathy with persistence viral presence. Modified from Kuffner et al. [60].
Hepatitis C virus

Hepatitis C virus (HCV) is a hepatotropic small enveloped, positive sense, single-stranded RNA virus in the Flaviviridae family and genus hepacivirus [63,64]. The main route of transmission is parenteral exposure via blood or blood components, and a majority of intravenous drug users may become infected by repetitive exposure to contaminated injection equipment [65]. The virus is responsible for 15% to 20% of cases of acute hepatitis. After acute infection, about 50% to 80% develop chronic infection [64]. A subset of patients with chronic hepatitis are at increased risk of developing fatal complications such as cirrhosis (20%) and hepatocellular carcinoma (4%-5%) [63-65]. The involvement of HCV in extrahepatic manifestations such as insulin resistance, Type 2 diabetes mellitus, glomerulopathies and oral manifestations have been described in epidemiological studies [64]. Although cardiac involvement in HCV infection is rare, contested data implicates the virus as an aetiologic agent in some cases of viral CM. [66]. Fulminant MC with congestive HF, hypotension and death may be a consequence of HVC infection but very rare [67,68]. A recent study of 48 non-ischemic DCM patients and depressed systolic function chronic HCV found 4.8% had serum antibodies to the HVC and 2.4% with HCV RNA [69]. Characteristics pathologic features associated with HVC infection include minute foci of necrosis of isolated muscle bundles usually surrounded by lymphocytes and diffuse serious inflammation [70]. The ventricles may also be dilated with petechial haemorrhages [68,70].

Influenza virus

Influenza virus is an enveloped single stranded, negative-sense, helically shaped RNA virus. The virus belongs to the Orthomyxoviridae family and classified into three distinct types (A, B and C) but only A and B has human latency reservoir [71,72]. Transmission pathway include direct contact with infected nasal discharges, contact with fomites (contaminated objects such as towels or hairbrush) and inhalation of virus-laden aerosols. It is the primary aetiologic agent of sporadic and epidemic cases of influenza disease [73]. Cardiac involvement and clinical MC are uncommon in people infected with influenza. However, pre-existing cardiovascular diseases significantly increases the risk of morbidity and mortality in infected patients [74]. In periods of influenza epidemic, about 5% to 10% of infected patients may exhibit symptoms of cardiac involvement [75]. Autopsy findings in fatal cases show biventricular dilatation with mononuclear infiltrate particularly in perivascular area [76]. Although the prevalence of influenza A and B IgG antibodies is high in DCM patients, positive PCR findings in EMB is rare (< 0.5%) [7,77].

Poliovirus

Poliovirus is a member of Enterovirus C, in the family of Picornaviridae. It is a single-stranded positive sense RNA genome [78]. Transmission route of poliovirus is via oral contact with secretion or fecal material from the infected person. Most infection cause asymptomatic viral replication limited to the alimentary canal. Gastrointestinal tract, including the pharyngeal mucosa, is both the portal of entry and primary locus of infection, and the source of viral dissemination [79]. Infection causes poliomyelitis disease, a paralytic disease but 99% of the disease has since been eradicated following the introduction of the polio vaccine [80]. Myocardial involvement after poliovirus infection is very rare, reported in studies in the 1950s with almost no case reports on myocarditis in poliomyelitis in recent years, possible due to successful efforts in eradication of poliomyelitis [81-83].

Mumps virus

Mumps virus is a member of the Paramyxoviridae family of enveloped, non-segmented, negative-sense RNA viruses. Humans is its only natural host. The virus is highly neurotropic, with evidence of CNS infection in approximately half of cases [84]. The virus causes mumps – a contagious disease that spreads from person to person through respiratory secretions. Before routine vaccination, 95% of adults has serological markers of exposure, which dramatically reduced after the introduction of vaccination. Characteristics of mumps disease are painful swelling of the parotid glands, but can also involve numerous other tissues and organs, resulting in inflammatory reactions including encephalitis, meningitis, orchids, myocarditis, pancreatitis and nephritis [84]. Only about 10% of cases exhibit complications with the involvement of other organs including the heart. Cardiac involvement is a rare complication since the development of mumps vaccine and when observed is described as either pericarditis or acute endocarditis [85]. Myocarditis is rare but a known complication of mumps, with earlier reported incidence of 4-15% [86]. Myocarditis occurs in the first week of the disease and ECG abnormalities usually disappear few weeks later [86].

Rubella virus

Rubella virus belongs to the Togaviridae family and the only members of the Rubivirus genus of enveloped, positive sense, single stranded RNA virus. Its main transmission pathway is respiratory aerosols to the nasopharyngeal infection and transplacental mother-to-foetus infection. The main site of viral infection and dissemination is the upper respiratory tract and nasopharyngeal lymphoid tissue [87]. Infection by rubella virus causes rubella disease (German measles) and congenital rubella syndrome or miscarriage if rubella infection occurs during the first trimester [88]. Complications of rubella virus include arthralgia or arthritis, encephalitis and haemorrhagic manifestations as well as orchitis, neuritis, and late syndrome of progressive panencephalitis [87]. The incidence of myocardial involvement in post-rubella infection is extremely limited. Reported cases suggest neonatal rubella myocarditis is common due to teratogenicity of rubella virus for developing organs of the human embryo [89].

Rubeola virus

Rubeola virus belongs to the Paramyxoviridae family and of the Morbillivirus genus of an enveloped, single-strand, non-segmented negative sense RNA virus. Humans are the only reservoir and has a single serotype [90]. It is highly communicable and spreads through aerosols, direct contact with nasal or throat secretions and less frequently by contact with contaminated surfaces. Once inhaled and a primary target cell (respiratory epithelial cell) is infected, systemic spread ensues and clinical signs appear after 9 to 19 days. Primary infection by rubeola virus causes measles, which is more acute in infants and older people than in children, and rarely causes death [90,91]. Infection confers life-long immunity where second attacks are described as errors in the diagnosis of either the first or the second illness [90]. In rare cases, severe measles-associated CNS complications may occur – acute disseminated encephalomyelitis, measles inclusion body encephalitis or subacute sclerosing panencephalitis [91,92]. Data on the incidence of cardiac complications following measles is extremely limited. Myocarditis and heart block may be common presentation of cardiac abnormalities in measles [93,94].
Variola virus

Variola virus belongs to the Poxviridae family of the Orthopoxvirus genus of enveloped, non-segmented linear double stranded DNA viruses [95]. The common human exposure routes are inhalation of aerosol through close contact, from fomites or contact with infectious materials in scabs [96]. Infection by variola virus causes smallpox, acute, self-limited human illness with no known human or non-human reservoir. However, the disease was eradicated from the human community towards the end of the 20th Century using vaccinations but mechanisms responsible for the emergence of new dangerous pathogens remain unknown [95,96]. Smallpox-associated cardiac involvement is lacking. However, the use of variola vaccines has been related with serious sequelae mostly myocarditis and pericarditis [97]. Of 450,000 military personnel in the use received variola virus vaccination between 2002 and 2003, two confirmed and 50 probable cases of vaccination-related myocarditis were reported (1.16%) [98]. The majority of cases of myocarditis resolve completely but some patients may develop chronic heart failure and even death [97].

Epstein-Barr virus

The Epstein-Barr virus, also known as human herpes virus 4, is a gamma-herpes virus that infects the majority of the world’s population [99]. It is one of the most successful viruses infecting more than 90% of humans with lifelong latency. Infection often occurs by contact with oral secretions. The primary site of infection and dissemination is epithelial cells in the oropharynx and almost all seropositive individuals actively shed virus in the saliva [100]. Infection with Epstein-Barr virus is often asymptomatic but may lead to a range of pathologies including infectious mononucleosis to severe cancers of epithelial and lymphocytic origin. Epstein-Barr virus has been detected in tissues from patients with nasopharyngeal carcinoma as well as associated with non-Hodgkin's lymphoma and oral hairy leucoplaikia [100-101].

Mycoplasma virus

Little data exists on mycoplasma virus. Mycoplasma are a group of microorganisms of the class Mollicutes, previously known as pleuro pneumonia-like organisms. Mollicutes have been shown to carry DNA viruses [117,118]. Morphologically they occur as rods, polyhedrons with short or long tails and as enveloped spheres resembling non-lytic animal viruses and now placed in the new family of bacterial viruses, the Plasmaviridae [118]. Mycoplasma viruses play a more significant pathogenic role in viral diseases than was previously realized, which were observed in a majority of HIV-infected patients suspected to play a synergistic role [119]. Mycoplasma virus causes pneumonia mostly in schoolchildren usually as a co-infection with bacteria [120]. There is very limited data on cardiac involvement following mycoplasma viral infection. Case reports suggest symptomless and transient manifestation in children [121,122].

Psittacosis virus

Studies and case reports of psittacosis virus are extremely rare with a majority of the available literature dating as far back as the 1950s. Early studies based on serological tests identified two strain of the psittacosis virus: the first originating from pigeons designated as pigeon ornithosis, and the second of an unknown origin [123]. Psittacosis is a latent infection of psittacine birds transmissible to humans causing atypical pneumonia, characterized by high fever stimulating a typhoidal state and symptoms of an atypical pneumonia [124,125]. Rarely, the disease may be transmitted from infected human to another [124]. Cases of myocarditis associated with psittacosis virus are rare and reported cases involve a combination of psittacosis virus and bacteria [126].

human immunodeficiency virus

Infection with the human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS), manifesting as a profound immunosuppression due to predominant selective depletion of helper/induce T lymphocyte expressing the receptor for the virus (the CD4 molecule) [127]. HIV infection has a high tropism for the brain resulting in neuropsychiatric abnormalities. In addition to inducing cell apoptosis, HIV infection may interfere with T4 cell function. HIV may exist in a latent or chronic form that may be converted to an active infection by a variety of inductive signals [127]. In HIV-infected individuals, cardiac involvement occurs in about 25 to 50%, with clinical heart disease in about 10% [128-136]. Congestive HF with LV dilatation and dysfunction is a common occurrence [137,138]. Endomyocardial biopsy (EMB) evaluation of specimen from 83 HIV-
DCM and 80 idiopathic DCM patients reveal a greater mean intensity of tumour necrosis factor - alpha (TNF-α: 0.81) and inducible nitric oxide synthetase (iNOS: 1.007) staining compared to idiopathic DCM (0.44 and 0.49 respectively). The staining intensity of TNF-α and iNOS had an inverse correlation with CD4 count. Staining intensity of iNOS was higher in HIV-DCM patients with HIV/CVB3 or HIV/CMV, which correlated with mortality rate [139].

**Arbovirus**

Arboviruses belong to the family of viruses transmitted by arthropods (insect vectors) or spread as zoonoses. In the U.S., arboviruses that cause human encephalitis are members of the *Togaviridae*, *Flaviviridae*, and *Bunyaviridae* families [140,141]. Mosquitoes are the main vectors but other biting flies, midges and ticks may also transmit the disease. Humans are incidental hosts who do not produce significant viremia and do not contribute to the transmission cycle. Humans acquire infection during blood feeding by an infected arthropod although laboratory acquired infections may also occur after handling tissues and body fluids [140]. Besides encephalitis, epidemic mosquito-borne arboviruses include yellow fever, dengue, West Nile, chikungunya and Zika virus [140,141]. At present, cardiac complications associated with arbovirus infection is rare. However, case reports in the 1970s describe myocarditis, pericarditis and cardiomyopathy associated with dengue and chikungunya viruses [142,143]. In the 1960s and 70s, dengue-associated myopericarditis was common in Ceylon with ECG abnormalities but with no clinical involvement of the heart [143]. Dengue associated myocarditis has favourable prognosis with resolution of symptoms, improvement in ECG and no residual cardiomegaly but in a few cases may lead to after handling tissues and body fluids [140]. Besides encephalitis, epidemic mosquito-borne arboviruses include yellow fever, dengue, West Nile, chikungunya and Zika virus [140,141]. At present, cardiac complications associated with arbovirus infection is rare. However, case reports in the 1970s describe myocarditis, pericarditis and cardiomyopathy associated with dengue and chikungunya viruses [142,143]. In the 1960s and 70s, dengue-associated myopericarditis was common in Ceylon with ECG abnormalities but with no clinical involvement of the heart [143]. Dengue associated myocarditis has favourable prognosis with resolution of symptoms, improvement in ECG and no residual cardiomegaly but in a few cases may lead to persistence symptoms, cardiomegaly and ECG abnormality transiting to cardiomyopathy [142]. Recently, Zika virus outbreak has been reported in the U.S. and a first travel acquired Zika acute infection complicated in myocarditis to mainland France, which recommends ECG and troponin assessment if any cardiac symptoms are present in a patient with acute Zika infection [144].

**Pathogenesis of cardiac damage**

**Damage to the cardiomyocyte**

Despite the availability of a well-characterized experimental models and common acceptance that viral infection causes myocarditis, the exact mechanisms underlying pathogenesis in humans remain controversial. At present, the only available evidence comes from animal models of enteroviral MC, which demonstrate a tri-phasic pathogenic process: (a) direct virus-mediated damage; (b) immune-mediated damage; and (c) myocardial remodelling and cardiomyopathy [145-151].

**Phase one: Viral-mediated damage**

Cardiac involvement after viral infection begins when viruses invade the cardiomyocytes or macrophages through binding with specific receptors and co-receptors. The receptor for CVB and adenovirus 2 and 5 is the hCAR (a junctional protein), which has been supported by the observation that the absence or low abundance of hCAR prevents viral invasion of the cardiomyocytes [152,153]. A co-receptor playing a role in viral invasion for serotypes B1, B2 and B5 is the CVB co-receptor decay-accelerating factor (DAF) [154]. Differential binding to this receptor influences viral virulence [155]. Other determinants of the virulence of CVB include variation in viral genome, and host factors such as selenium deficiency and mercury exposure [156-159]. To obtain a complete understanding of viral-mediated damage to the myocardium, future studies should investigate genetic and environmental determinants of virulence to understand why a great majority of cardiotropic viruses including enteroviruses, adenovirus and parvovirus do not cause cardiomyopathy.

The initial acute phase of active viral replication lasts for a few days in which direct viral damage of the cardiomyocytes occur via virus-mediated lysis [160]. The virus first degrades cell structures to enable entry and damage to the cardiomyocyte [161]. When this damage occurs in the complete absence of host immune, viral proliferation alone is sufficient to initiate severe acute MC with resultant DCM and HF [160]. The innate immune response is the first line of defence against the initial viral invasion. Viral particles and certain host proteins triggers an innate immune response, which involves toll-like receptors (TLRs) and pattern recognition receptors in patients with tissue injury [162]. These receptors recognize foreign antigens and trigger the activation of nuclear transcription factors leading to the production of inflammatory cytokines [163]. In response to massive cytokine production, natural killer (NK) cells and macrophages migrate to the heart and minimize viral propagation mostly through direct cytotoxic effect [164]. In clinical practice, this initial phase is often asymptomatic because innate immune response prevents initial myocardial damage by eliminating the virus and renovating the damaged tissues [165]. However, in immunocompromised patients, the acute phase of viral replication may present with fever, weakness, rash, muscle pain and joint pain. It may also be accompanied by symptoms of respiratory or gastrointestinal viral infection [150].

**Phase two: Viral mediated immune damage**

In immunocompetent patients, immune response stimulated by certain host proteins limits viral replication, and in the majority of patients, eliminates the virus from the host. However, immune response itself can cause myocardial damage. In this case, the balance between beneficial and detrimental effects of immune response significantly influences the extent of myocardial cell loss [151]. The characteristics of this second (sub-acute) phase of the pathogenesis of viral CM is viral mediated immune damage to the myocardium, which may last for weeks to months.

This phase is characterized by the production of antibodies (T- and B-lymphocytes), which peak at 7-14 days after virus inoculation, which represents the most severe phase of myocardial damage [151]. These antibodies produced to destroy viral particles may also react with cardiac structure to cause damage to the myocardium. The cytotoxic T-lymphocytes response is the most important mechanism responsible for lysis of virus-infected cells as well as responsible for autoimmune-mediated myocardial damage [150]. The cytotoxic T-cells may attack virally infected cardiomyocytes because of molecular mimicry – myocardial antigens that bear similarities to viral proteins may cause T-cells originally aimed at the virus to cross-react with host antigen and produce myocyte damage. The products of cardiac cell destruction themselves may then stimulate further lysis by T-cells [166]. Murine models have also suggested host-depending genetic factors may increase the risk of autoimmune reactions [148].

A combination of direct viral injury, cytokine context and the level of pro-inflammatory immune reaction determine the severity of MC and the possibility of viral infection shifting from acute to sub-acute phases [164]. The activation of acquired immunity results in chronic inflammatory response in the myocardium and may lead to organ dysfunction due to fibrosis and myocardial remodelling. It may also
cause damage due to necrosis and switching on the autophagy of the cardiomyocytes. Although viral genome has been detected in cardiac tissues of patients with chronic MC, the mechanism of long-term persistence of CVB in the presence of intact immune system remains unknown [164,167]. In clinical practice, patients in this second phase may present with dyspnoea, chest pain, heart palpitations, increased exercise intolerance, increased sweating and fainting [148].

**Phase three: Cardiac remodelling and myopathy**

The third phase of the pathogenesis of viral CM that involves cardiac remodelling and myopathy has been the most difficult to elucidate. The controversy of whether the present of persistent viral genomes in the myocardium or remnants of previous infection contribute to the progression to CM remains unclear. In this third phase, it is usually not possible to detect the virus in the myocardium. In the case of persistence inflammatory response, the heart may develop idiopathic DCM due to myocardial remodelling [148]. Antibodies acting on the sarcolemma, myeloma, beta-receptors, acetylcholine receptor, Laminin and cardiac conduction tissue may play a pathogenic role but the participation of antibodies against fibrils, stress proteins and intermediate filament remains unclear [168]. Inflammation may be followed by the release of cytokines (the transforming growth factor) and the activation of metalloproteinase. Patients with VMC exhibit over expression of the Matrix metalloproteinase (MMPs), which can degrade different components of the cardiac tissue and contribute to myocardial remodelling [169]. Other complementary mechanisms that may play a role in post-inflammatory myocardial remodelling include enhanced fibrosis, which is a consequence of osteopontin and matricellular protein Cyr61 activity [170]. Post-inflammatory cardiac remodelling and myopathy may present with LV systolic dysfunction and LV wall hyperkinesia correlating with ECG abnormalities such as ST-S changes. RV dysfunction is rare. Formation of thrombi within cardiac cavities and pericardial effusion can also occur [148].

Autoantibodies cross-reactivity due to antigen mimicry is another proposed pathogenic mechanism contributing to myocardial remodelling. In patients with lymphocytic MC or DCM, autoantibodies to a variety of antigens is a common histological finding [171,172]. The virus CVB shares epitopes with cardiac myosin (which is an intracellular antigen) and cross-reactive antibodies may lead to the production of autoantibodies due to this antigen mimicry [173,174]. Thus, following virus clearance from the myocardium, cardiac myosin may provide an endogenous source of antigen in chronic MC and stimulate chronic inflammation through autoimmune mechanisms. Antone et al. and Huber et al. have described cross-reactivity between cardiac myosin and endogenous human cell-surface protein Laminin to suggest that Laminin may serve as an ongoing stimulus in chronic antibodies to cardiac myosin cross-reaction with beta-adrenergic receptor, which may contribute to cardiomyocyte apoptosis [172,175,176]. However, the main challenge has been distinguishing antibody autoreactivity occurring in the course of normal immune reaction from that of autoimmune disease in which anti-cardiac antibodies contribute to ongoing CM.

Histologically determined viral presence or viral components in the myocardium independent of local immune response may also lead to fibrosis, hypertrophy and the degeneration of cardiomyocytes, which is observed in DCM patients [177]. Protein products of the enteroviral genome can cleave host proteins, including dystrophin, leading to CM [178]. This induction of dystrophin deficiency augments CM that accompanies the enterovirus [179]. Experimental models indicate CVB might persist in the myocardium with partially deleted genome leading to low-grade non-cytolytic chronic cardiac infection [180]. These findings, if replicated in human DCM patients, might be useful to understand how enterovirus infection can cause chronic DCM in the absence of MC [181]. Pathological changes in the myocardium may provoke chest pain, tachycardia, irregular heartbeat, dyspnoea at rest and during exertion, swelling of lower limbs, fainting and hyperhidrosis [148].

**Damage to the vascular endothelial cells**

In contrast to enteroviruses and adenoviruses, which infect and injure cardiomyocytes, other common cardiotropic viruses in VMC and VCM such as erythroviruses (parvovirus - HPVB19 and HPVB19V) or human herpesvirus (CMV and HHV6) infect the vascular endothelial cells (ECs) [182-186]. Biopsy samples show parvovirus PVB19 is localized in the ECs of venules, small arteries or arterioles in patients with fulminant MC or acute onset of HF [182] and in the ECs of small capillaries in patients with chronic inflammatory CM [183,184]. The primary erythroviruses infection occur predominantly in childhood and the virus persists in the bone marrow of healthy individuals with no recognized clinical significance.

Infection and replication of parvoivirus B19 infection is restricted to the erythroid progenitor cells but may also affect the ECs through the distribution of the primary erythroviral receptor (P antigen), and co-receptors like the integrin α5β1 and the KU80 protein [187-189]. The pathogenic mechanisms of ECs damage and the primary erythroviruses infection occur predominantly in childhood and the virus persists in the bone marrow of healthy individuals with no recognized clinical significance. HHV-6 on the other hand is a lymphotropic virus with tropism mainly for CD4+ and CD8+, B-cell and NK cells but can also infect the vascular ECs [197,198]. HHV-6-specific DNA has been observed in the vascular ECs both in vivo and in vitro to suggest the virus damages the EC [198-200]. It has been postulated that ECs and cardiac myocytes may be important reservoirs for viral latency and re-activation [198]. For HHV-6 and other herpes virus, frequent activation occurs mainly through infections or drugs with sub-acute clinical presentations particularly in acquired or drug-induced immune-deficiencies such as transplant recipients or patients with autoimmune disorders. Mostly, cardiac infection by the HHV-6 enhances the pathogenicity of other viruses more than being a pathogen itself [196]. Viral infection in the ECs may lead to a worsening clinical picture because of microvascular dysfunction, which may predict long-term disease progression in chronic HF [201-204]. Parvoviruses and herpesviruses may also cause cardiac damage through infecting interstitial tissue resulting into heart dilatation and LV dysfunction, and ultimately HF [148].

**Clinical manifestation and investigations**

**Clinical presentation**

Viral cardiomyopathy has a wide spectrum of clinical presentation ranging from asymptomatic course of a mildly ongoing disease with slightly impaired myocardium to a severe fulminant HF accompanied...
by malignant arrhythmias. Presentation also varies from one phase of the disease to another. Sudden cardiac death (SCD) may also be the first clinical presentation of the disease in previously healthy individuals [196]. The subclinical nature of the disease during the period of acute viral infection does not exclude a possible evolution of inflammatory myocardial damage while mild symptoms do not indicate favourable long-term prognosis. The extent of myocardial damage in the acute phase may be a determining factor for the recovery of LV function in subsequent phases. Despite the wide heterogeneity, clinical presentation of patients with viral CM often include HF, chest pain and arrhythmias [205-207].

Heart failure

Heart failure is the most common clinical manifestation of viral CM. Although the onset is usually gradual with mild symptoms, in the case of fulminant MC, the development of HF is acute resulting in cardiogenic shock requiring mechanical circulatory support (device therapy) or cardiac transplantation to save the patient’s life. Patients who survive the acute phase show a significant improvement or complete normalization of LV systolic function with favourable long-term prognosis in a few weeks [165]. Thus, the decision for long-term treatment options such as cardioverter, defibrillator, resynchronization or cardiac transplant should be considered after the lapse of the acute phase.

Chest pain

New onset or worsening chest pain either at rest or during exertional activities is an important clinical presentation in patients with viral heart infection. Patients with viral infection of the endothelium may have a higher incidence or worsening chest pain as a manifestation of acute viral heart disease [112]. Usually, chest pain mimics angina pectoris or has pericarditis-like character in the presence of perimyocarditis [58].

Arrhythmias

Arrhythmias is another common complaint and a reason for a visit to a physician. In patients with viral heart disease, arrhythmias may present as supraventricular or ventricular arrhythmias, conduction disturbances or serious ventricular arrhythmias suggesting the possibility of giant cell myocarditis or cardiac sarcoidosis. Symptoms may be present in one patient simultaneously or manifest at different phases of the disease. Symptoms of HF meeting the criteria of inflammatory CM indicate an unfavourable prognosis compared to symptoms of chest pain and arrhythmias [148].

Clinical investigations

Clinical diagnosis of viral CM relies on the current evidence and expert consensus guidelines for the diagnosis of MC, which is a common consequence of acute viral heart infection. Diagnosis of MC is per exclusionem. The AHA statement on diagnosis of forms of DCM and the ESC guidelines on myocardial and pericardial disease recommend that MC should be suspected in the presence of (a) acute chest pain; new onset or worsening dyspnoea [3,205]; (b) palpitations or unexplained arrhythmias; and (c) unexplained cardiogenic shock. Diagnostic criteria for MC is a combination of clinical findings: ECG abnormalities, the presence of myocardial infarction markers, functional/structural abnormalities and tissue characterization by cardiac magnetic resonance imaging (Table 2). The AHA and ESC recommend that clinical diagnosis of MC should be suspected in the presence of the following clinical presentation and/or diagnostic criteria [3,205].

1. ≥ 1 clinical presentation and ≥ 1 diagnostic criterion
2. ≥ 2 diagnostic criteria, if the patient is asymptomatic

Blood tests

Currently, clinically available and specific blood tests are non-specific and cannot confirm the diagnosis of MC. Serum markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein may be elevated in MC but are non-specific. Biomarkers of cardiac injury such as levels of troponin 1 may be elevated especially in patients with acute and clinically severe MC who require hospitalization but current evidence is inconsistent. In a clinical trial in the U.S. involving subjects with histologically acute MC with an average of one-month symptoms, only 34% of the patients had elevated levels of troponin 1 [3, 205,208]. However, the current troponin assays such as soluble ST2 (a clinically available serum biomarker that also reflects inflammation) promise to be more useful in the diagnosis of MC. The ESC working group position statement recommends troponin levels should be obtained in the clinical setting of suspected MC patients, while the AHA position statement recommends assessment of natriuretic peptides and other biomarkers [3,205].

Electrocardiography

Electrocardiogram (ECG) is a simple conventional examination useful for the initial evaluation of diseases in cardiology. The common ECG abnormality in viral CM are non-specific T-wave changes [209]. Sometimes, the ECG abnormalities may mimic acute myocardial infarction or pericarditis with ST segment elevation, ST segment depression, PR segment depression and pathological Q-waves [210-211]. Often, tachyarrhythmias are non-sustained and rarely result in haemodynamic compromise in adult patients with viral CM. While the prognostic significance and optimal management of non-sustained ventricular tachycardia in acute MC remain unclear, Q-waves and widened QRS complex including left bundle branch block may indicate

Table 2. Clinical presentation and diagnostic criteria for viral myocarditis

| Clinical Presentation | Diagnostic Criteria |
|-----------------------|---------------------|
| Acute chest pain, pericarditis or pseudoischemic | ECG abnormalities (AV block, BBB, ST/T-waves changes, supraventricular/ventricular arrhythmias, low voltage QRS complex and abnormal Q waves) |
| New onset (days to 3 months) or worsening dyspnoea at rest or during exertion and/or fatigue with/without sings of left/right HF | Markers of myocardial necrosis (elevated cardiac troponins or CK-MB) |
| Subacute/chronic (> 3months) or worsening of dyspnoea at rest or during exertion and/or fatigue with/without sings of left/right HF | Functional/structural abnormalities in echocardiography or MRI (impaired LV/RV function with/without LV/RV dilatation, increased ventricle wall thickness, pericardial effusion and intracardiac thrombi) |
| Palpitation and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death. | Tissue characteristic by CMR (presence of at least 2 of 3 Lake Louise criteria, myocardial oedema and early and late gadolinium enhancement) |

AV: Atrioventricular; BBB: Bundle Branch Block; ECG: Electrocardiogram; MRI: Magnetic Resonance Imaging Adapted from AHA Scientific Statement on Diagnosis and Management of Specific DCM [3]
Echocardiography

Echocardiography is a useful low-cost non-invasive imaging modality for excluding other causes of HF as well as for detecting ventricular thrombi. However, echocardiography has no pathognomonic features to use for the diagnosis of patients with viral MC [215,216]. Segmental wall abnormalities may mimic those of myocardial infarction [217]. Patients with fulminant MC may present with a more normal chamber dimension and thickened walls compared to patients with less acute MV who exhibit a greater LV dilation and normal wall thickness [218]. LV dysfunction is rare but an important predictor of death or heart transplantation [219]. New echocardiography imaging techniques such as strain echo may have better specificity for MC [196].

Magnetic resonance imaging

Cardiovascular magnetic resonance imaging (CMRI) is useful in patients suspected with MC to localize and quantify the extent of tissue injury including oedema, hyperaemia and fibrosis [220]. Recently, CMRI alone has been shown to confirm correct diagnosis in 80% of a series of 82 patients with biopsy-proven MC [221]. However, diagnosis requires both T1 and T2-weighted imaging to achieve optimal sensitivity and specificity. In contrast to older evidence, CMRI abnormalities do not correlate closely with EMB evidence of MC [204]. When ≥ 2 Lake Louise criteria are positive, myocardial inflammation may be predicted with a diagnostic accuracy of 78%, which drops to 68% with the use of delayed post-gadolinium enhancement [196]. Additional prospective clinical studies evaluating prognostic values of CMRI are needed to determine whether tissue characterization may complement management or outcome of MC patients [220].

Endomyocardial biopsy

Confirmatory diagnosis of MC still requires histological or immunological evidence of inflammation in cardiac tissues. When performed by highly experienced operators, EMB can have very low major rate of complications, and LV biopsy is as safe as RV biopsy [204,222]. However, there are differences in the indications for EMB by the 2013 AHA/ACCF/ESC joint statement and the 2013 ESC guidelines on HF management working group [205, 223]. The ESC position supports broad use of EMB for the diagnosis and management of MC based on the presence or absence of viral genomes and inflammation. The AHA/ACCF/ESC statement recommends performance of EMB in two group of patients. (1) In patients with HF and normal/dilated LV, > 2 weeks of symptoms and haemodynamic compromise. (2) In patients with dilated ventricle, 2 weeks to 3 months symptoms, new ventricular arrhythmias or Mobitz type II second-degree heart block or those who fail to respond to usual care within 1 to 2 weeks of treatment [223,224]. EMB-based criteria – presence of inflammation by immunohistology and viral genomes absent by PCR – have been used to define a cohort of patients with chronic DCM who responded to immunosuppression therapy [225]. Despite the diagnostic value of EBM, current recommendations support its use only in clinical scenarios where the incremental prognostic and therapeutic information gained outweighs the risk and cost, which varies by medical centre depending on availability of necessary facilities and expertise [205,223].

Clinical management

The pathogenic mechanisms of cardiomyocyte destruction are direct viral damage, anti-viral immune response or autoimmune injury [145-151]. In adults, cardiomyocytes rarely regenerate and recovery of myocardial function depends on the residual myocardial tissue. Thus, response to treatment of acute and chronic MC depends on the specific causes of the disease, severity of irreversible tissue damage at the onset of treatment and the potential of the myocardium to compensate such processes (Figure 2). If pre-treatment damage is severe, aetiology specific treatment options is strongly recommended to prevent rapid progression of the disease but would not achieve significant improvement in ventricular function [196]. Based on current guidelines, the recommended treatment options includes standard HF therapy, antiviral therapy, immunomodulatory therapy and immunosuppression therapy based on the absence of biopsy-proven inflammation, positive PCR viral genomes, and the persistence of HF symptoms > 3 months or > 3 weeks of therapy (Figure 2). For patients with non-responsive HF symptoms, device therapy (implantable cardioverter defibrillator, cardiac resynchronization therapy or ventricular assist device) depending on individual patient characteristics should be considered.

Heart failure therapy

The mainstay of treatment for viral MC presenting as DCM with LV systolic dysfunction is the conventional HF medical therapy. The current AHA/ACCF and ESC HF guidelines recommend angiotensin-converting enzyme-inhibitor (ACE-I)/angiotensin receptor blocker (ARBs) and/or beta-blockers [133,226]. Experimental murine myocarditis models show ACE-I (captopril) and ARB (candesartan) relieve HF symptoms in MC patients [227,228]. In patients presenting with myopericarditis-like syndrome of chest pain and normal or near normal of ventricular function, non-steroidal anti-inflammatory drugs such as indomethacin should be avoided because of the risk of increased inflammation and mortality [229]. In addition to guideline-based medical therapy, patients with acute MC should refrain from competitive athletics for 3 to 6 months after diagnosis of viral infection or after documented ventricular recovery by non-invasive imaging modalities [3,196].

Antiarrhythmic therapy

Ventricular arrhythmias are common in patients with active viral heart infection but in most cases do not require specific therapy. However, patients presenting with severe refractory ventricular arrhythmias may require antiarrhythmic therapy while patients with spontaneous remissions may be candidates for long-term antiarrhythmic therapy (amiodarone or ICD) only after all options for controlling arrhythmias have proved unsuccessful [133,226]. Patients with atrioventricular block may need a temporary pacemaker but usually atrioventricular block is transient and indication of permanent pacemaker is rare [226].

Antiviral therapy

The treatment target of antiviral therapy is the elimination of viral translation, transcription and proliferation usually during the initial acute phase of viral infection and replication. Antiviral medication work by preventing viral attachment to host-cells receptors, virus entry or virus uncoating. Medications such as Pleconaril, W1N 54954, or soluble CAR-Fc are only effective during the early stages of the disease. Since, most adults presenting to physicians are in the chronic phase of the disease, the use of antiviral therapy is limited in patients with viral heart diseases. A second challenge of antiviral therapy in patients with viral heart infections is the timing of treatment to prevent progressive myocardial damage by viral clearance before chronic infection causes irreversible damage to myocardial tissues [196,230].
Immunotherapies

Immunotherapies work by modifying immune system to reduce autoimmune-mediated damage to the myocardium during the chronic phase of viral heart infection. Although the evidence to support their use in clinical practice is inconclusive, immunomodulation, immunosuppression and immunoadsorption show promising value in LV function improvement and HF symptoms resolution.

Immunomodulation

Interferon-beta (IFN beta) is an immunomodulatory agent that serve as a natural defence against many viral infections. Innate production of interferon is associated with clinical recovery from viral infection and subsequent sequelae while exogenous administration with protective effect. IFN beta-1 constitute a promising option for treatment for chronic viral heart disease. At present, treatment for chronic viral heart disease is lacking but evidence from uncontrolled open label phase II trials demonstrate sub-groups of patients non-responsive to optimal medical therapy for HF may significantly benefit from 6-months IFN beta-1 medication and HF medication even years after the onset of chronic disease [152,186]. Patients with persistence enterovirus and adenovirus myocardial infection responded well to a 6-months treatment with IFN beta-1 and biopsy-proven complete viral genome elimination three months after termination of antiviral therapy. Viral clearance was accompanied by improved LV function, decreased ventricular size, relief of HF symptoms and decreased infiltrating inflammatory cells [152]. The IFN beta-1 therapy was well tolerated without any unexpected cardiologic or non-cardiologic side effects.

Frequent side effects of IFN beta include influenza-like symptoms and injection site erythema but vanish during the first week of treatment. Patients with severe LV dysfunction (LVEF <25% on IFN beta therapy require echocardiography monitoring because of complaints of mild worsening of HF symptoms due to wall oedema, a slight increase in LV dimension and minor deterioration of LVEF . These complaints disappear within 1 to 2 weeks followed by continuous improvement in HF in about less than 40% of patients [186]. PVB19 and HHV-6 do not affect myocardial contractile cells and thus respond less well on IFN beta treatment with respected to viral clearance and haemodynamic changes. Complete viral clearance for enterovirus and adenovirus suggest that early biopsy-based diagnosis and timely IFN beta treatment may prevent disease progression and consequently outcomes of chronic viral CM [196].

Immunosuppression

Inflammatory processes in the myocardium caused by pathogenic autoimmunity may survive virus elimination in the myocardium and warrant immunosuppressive therapy as a prophylactic for later immune-mediated myocardial damage [225,231,232]. Immunosuppressive therapy requires the exclusion of the virus from the patient based
on biopsy findings. Virus-positive patients do not benefit from anti-inflammatory therapy while virus negative patients with post-infectious or autoimmune inflammatory processes respond well. Frequently used anti-inflammatory drugs include immunoglobulins, corticosteroids, azathioprine, and cyclosporine administered for 3 to 6 months in addition to regular HF medication [225,232]. A randomized trial of 41 patients with immunohistologically biopsy-proven inflammatory CM and 2-year follow-up treated with corticosteroids and azathioprine for three months show sustained benefits in HF symptoms, LV dimensional and LVEF [232]. Noutsias et al. trial validated the diagnostic sensitivity and accuracy of the abundance of cell adhesion molecule (CAM) for inflammatory DCM even in the absence of lymphocytic infiltration because of a close functional association between the induction of CAM, and immunocompetent infiltration and cytokine induction [233]. Thus, CAM is a promising criterion for selecting patients who are likely to benefit from immunosuppressive therapy [233]. Current evidence suggest that immunosuppressive therapy in patients with biopsy-proven virus negative inflammatory CM, in addition to standard HF therapy, is both safe and efficacious. However, there is a need for larger trials powered to detect a difference in clinical endpoints such as HF hospitalization, transplantation and mortality.

Immunoadsorption

Current evidence supporting the use of immunoadsorption therapy such as intravenous immunoglobulin (IVIG) in patients with VMC is inconsistent. An earlier study on acute MC patients treated with IVIG associated high doses of IVIG with improved recovery of LV function and a tendency towards better survival during the first year of presentation [234]. However, a recent study comparing IVIG with cortisone (steroid) therapy reports IVIG is ineffective in children [235]. IVIG and cortisone have comparable effect on freedom from death at the first years and at fifth year and on the median time to recovery of LV function, suggesting IVIG alone confers no advantage to steroid therapy alone [235]. Despite inconsistent evidence, the rationale for serial treatment or high doses of immunoadsorption therapy is to lower cardiotoxic antibodies in the patient's plasma and prevent autoantibodies cross-reactivity with the host's intracellular antigen (cardiac myosin) that results in damage to myocardial tissue [174]. Favourable hemodynamic outcomes of immunoadsorption in DCM patients have been related to the elimination of functionally active cardiac autoantibodies evident in biopsy-proven reduction of lymphocytic infiltration and CAM expression [236]. Additional studies are warranted to clarify the therapeutic value of immunoadsorption in patients with VMC.

Meta-analysis of diagnosis and management

The importance of diagnostic methods in informing the selection of the most appropriate treatment emerges clearly in the treatment of VCM patients. At present, consensus guidelines by leading cardiology societies (AHA/ACC/ESC) discourages the use of EMB except in centres with the requisite expertise and experience because of the associated high risks of complications. Instead, they recommend that diagnosis should include a combination of clinical signs and symptoms, and the presence of ECG abnormalities, markers of myocardial necrosis, echocardiographic or MRI markers of cardiac functional/structural abnormalities and/or tissue characterization by MRI. However, the limited utility of EMB undermines effective clinical management strategies since it is the only reliable method for detecting and quantifying viral presence in the myocardium and for providing information useful for the selection of the most appropriate therapy. While standard HF therapy has proved beneficial in VCM patients with cardiac dysfunction, in a subset of VCM patients who have no demonstrable evidence of cardiac dysfunction or who have refractory symptoms despite optimal medical therapy for heart failure, safe and efficacious treatment has remained a major challenge [3,233]. Antiviral drugs, which target viral elimination in the acute phase, are inappropriate since most patients at presentation are already in the chronic stage of the disease [196].

Findings

In total, the 22 studies included in this meta-analysis enrolled 1,321 patients with either VMC or VCM with mean age of 33 years (range 3 to 60 years) with a greater proportion of male patients (60%) [62, 186,225,232,242-259]. Fourteen (14) studies were randomized controlled trials while the remaining eight (8) were retrospective cohort studies [62,225,232,242-244,246-259]. While randomized control trials provide strong evidence, observational studies provide actual experience of the application of findings in a clinical setting. Twelve studies assessed immunosuppression (prednisone, azathioprine, cyclosporine or corticosteroids), seven assessed immunoadsorption (immunoglobulin) and the remaining studies assessed immunomodulation (interferon beta) [62,186, 225,232,242-249,252-259]. Outcomes measured varied across studies with LVEF being a common feature followed by LV dimensions. Other common measures assessed in more than two studies included NYHA functional class, viral genomes clearance, and death and hospitalization.

Various diagnostic or inclusion criteria for patient selection were used by individual studies. However, the most common features included LV systolic dysfunction (measured as LVEF), the duration of symptoms usually longer than six months, refractory symptoms and biopsy-proven virus-free myocardium. In more than two studies, common clinical presentation were fever, shortness of breath, chest pain, palpitations (arrhythmias), pre-syncpe or syncpe (atrioventricular block), arrhythmia and HF. In almost all the studies, EMB was the most common method for quantifying inflammatory infiltrates (viral genomes), and together with symptoms duration (>6 months) was

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used as part of selection criteria in four studies [225,232,254,258]. Prolonged symptom duration potentially indicates non-responsiveness to HF therapy. However, cut off values of LV systolic dysfunction (LVEF) varied from as low as ≤ 30% to as high as ≤ 45%, and one study included DCM patients with HLA upregulation on biopsy specimens [135,150,232].

Pooled analysis of 11 studies showed that the addition of immunosuppressive therapies to standard HF therapy significantly improved LV systolic function in the short-term (6-12 months) [62,225,242,246,251,253,254,256,258,259]. Weighted mean difference (WMD) of LVEF at baseline and after 6 or 12 months of immunosuppressive therapy revealed a significant increase in LVEF (WMD: 8.61% 95% CI: 5.54% to 11.66%; p = 0.000). Figure 3). A greater improvement in LV function was also observed in patients receiving immunosuppressive therapy compared to patients receiving only standard HF therapy or placebo (WMD: 9.97%; 95% CI: 3.78% to 16.16%) (Figure 4). Immunosuppression was also associated with significant improvement in LV dimensions observed as reductions in LV end diastolic diameter (LVEDD) and volume (LVEDV) at baseline relative to after six months of treatment. LVEDV reduced by a weighted mean of -5.57 mm (95% CI: -8.85 to -2.29; p = 0.001) (Figure 5) and LVEDV reduced by -56.60 ml (95% CI: -88.82 to -24.39; p =

| 1st Author | Year | Study Methodology | Patients | Drugs | Patients/Entry Criteria | Main Findings |
|------------|------|-------------------|---------|-------|-------------------------|---------------|
| Parrillo [242] | 1989 | Randomized controlled | 59      | Prednisone | DCM/CHF: Biopsy evidence for inflammation and immoglobulin elevated erythrocyte sedimentation | Has marginal effect and should not be administered as a standard therapy |
| Latham [243]  | 1989 | Randomized controlled | 52      | Prednisone | Idiopathic DCM: Symptom duration < 2 years; LVEF ≤ 45% | No difference in mortality at 24 months |
| Chan [244]   | 1991 | Retrospective      | 13      | Prednisone + Azathioprine | Paediatric patients with biopsy-proven MC | Appears useful in improving clinical course and cardiac function with no adverse side effect |
| Drucker [245] | 1994 | Randomized to IVIG or no IVIG | 46     | Intravenous immunoglobulin | Acute CHF < 3 months, LVEF dysfunction due to myocarditis | High dose IVIG in acute MC improved LV function with a tendency of better survival |
| Balaji [246]  | 1994 | Retrospective      | 10      | Corticosteroids | Children with ventricular ectopic rhythm | Steroid treatment seems to benefit a subset of children with ventricular ectopic rhythms |
| Camargo [247] | 1995 | Randomized controlled | 43      | Prednisone + Azathioprine/ cyclosporine | Myocarditis and a LVEF < 45% | Improves prognosis of children with MC and severe LV dysfunction |
| Mason [248]   | 1995 | Randomized controlled | 111     | Prednisone + Azathioprine or cyclosporine | Paediatric population with histologically confirmed lymphocytic myocarditis | Improved survival and recovery of LV function |
| Lee [249]     | 1999 | Retrospective      | 36      | Intravenous corticosteroids | Paediatric population with histologically confirmed lymphocytic myocarditis | Improved survival and recovery of LV function |
| Ahdoot [250]  | 2000 | Retrospective      | 5       | Monoclonal OKT3 + intravenous immunoglobulin | Paediatric with acute MC and LVEF 5% to 20% | Reverses/inhibits immune response and improves myocardial function |
| Gullesstad [251] | 2001 | Randomized to IVIG of placebo | 40     | Intravenous immunoglobulin | Chronic HF > 6 months, LVEF < 40% | Reduced inflammatory effect and improved LV function |
| McNamara [252] | 2001 | Prospective placebo controlled | 62    | Intravenous immunoglobulin | DCM, LVEF ≤ 40%, symptoms < 6 months | In recent onset DCM, IVIG does not improve LVEF |
| Staudt [253]  | 2001 | Randomized crossover IA to IG | 25     | Immunoadsorption/ immunoglobulin | DCM patients, LVEF < 30%, evidence of autoantibody and inflammation | IA followed by IG mitigate myocardial inflammation in DCM patients |
| Wojnicz [252] | 2001 | Randomized to immunosuppression or placebo | 84    | Prednisone + Azathioprine | Inflammatory DCM + HLA upregulation on biopsy, symptoms > 6 months | Long-term improvement LV function, NYHA class |
| Frustaci [254] | 2003 | Retrospective responders vs. non-responders | 41     | Prednisone + Azathioprine | Biopsy proven virus negative Lymphocytic MC | Improved LV function and viral clearance |
| Kuhl [62]     | 2003 | Retrospective      | 22      | Interferon beta | LV dysfunction and EMB-evidence of myocardial virus persistence | Improved LV function and resulted in viral elimination |
| English [255] | 2004 | Retrospective      | 41      | Intravenous immunoglobulin + steroids | Children with biopsy proven MC and cardiac dysfunction and cardiotoxic viral infection | IVIG alone does not confer advantage to steroid therapy alone |
| Wojnicz [256] | 2006 | Randomized controlled | 74      | Artovastin | HF secondary to inflammatory DCM | Improved LV function |
| Frustaci [255] | 2009 | Randomized placebo controlled | 85     | Prednisone + Azathioprine | Virus-negative inflammatory CM | Improvement in LV function and dimensions |
| Klugman [257] | 2010 | Randomized to IVIG or no IVIG | 216    | Intravenous immunoglobulin | Paediatric myocarditis from paediatric discharges | IVIG did not confer a survival advantage regardless of patient's severity of illness |
| Schmidt-Lucke [186] | 2010 | Randomized to IFN beta and control | 23    | Interferon beta | Presence of virus genome and increased endothelial activation, HF symptoms > 6 months | Reduced endothelial damage |
| Escher [258]  | 2016 | Retrospective      | 114/53  | Prednisone + Azathioprine | EMB-proven virus -ve chronic MC of inflammatory DCM, LVEF< 45% | Short/long term improvement in LVEF and reduction in inflammatory infiltrates |
| Merken [259]  | 2018 | Randomized controlled | 180    | Prednisone + Azathioprine | Patients With virus-negative non-fulminating CM, symptoms > 6 months | Improved heart transplant-free survival and larger improvement in LVEF |

CM: Cardiomyopathy; DCM: Dilated Cardiomyopathy; EMB: Endomyocardial Biopsy; HF: Heart Failure; IA: Immunoadsorption; IFN: Interferon; IVIG: Intravenous Immunoglobulin; LV: Left Ventricular; LVEF: Left Ventricular Ejection Fraction; MC: Myocarditis
Figure 3. Forest plot of LVEF pre and post-immunotherapy

Figure 4. Forest plot for LVEF differences - immunotherapy and no immunotherapy

Figure 5. Forest plot of LVEDD pre and post-immunotherapy
0.001) (Figure 6). However, there was significant heterogeneity across individual studies due to differences in the characteristics of enrolled patients, the extent of depressed LVEF, the duration of symptoms, age of patients, myocarditis or DCM patients and the presence or the absence of inflammatory infiltrates in the myocardium. The effect of these differences were not considered in the present meta-analysis.

Pooled analysis of four studies reveal a tendency of immunosuppressive therapy improvement in cardiac function compared to patients on conventional therapy [232,242,251,256]. There was a reduction in the weighted mean of NYHA functional class (WMD: -1.76; 95% CI: -3.74 to 0.21) but it was non-significant (p = 0.08) (Figure 7). The significant heterogeneity across individual studies could be attributed to the inclusion of patients from all the functional groups (NYHA I – IV), since NYHA it was not part of selectin criterion in most of the included studies. Pooled analysis of three studies show immunosuppression therapy significantly reduced inflammatory infiltrates in the myocardium six months after commencing therapy (WMD: -5.90; 95% CI: -10.90 to -0.89) (Figure 8) [62,253,258]. The effect of immunosuppression on hard clinical endpoint of death and hospitalization or heart transplantation show a tendency towards a reduction in the events. Pooled analysis of six studies showed a non-significant reduction by 10% of deaths in the short-term (6 to 12 months) compared to conventional therapy or placebo (odds ratio [OR]: 0.90; 95% CI: 0.57 to 1.43; p = 0.67) (Figure 9) [225,248,252,255,257,259].
Pooled analysis of four studies also reveal a non-significant reduction of hospitalization by 20% in the short-term (6 to 12 months) compared to conventional HF therapy or placebo (OR: 0.80; 95% CI: 0.47 to 1.38; p = 0.43) (Figure 10) [225,252,255,259]. There was no heterogeneity observed across studies while analyzing deaths and hospitalization.

**Discussion**

**Clinical investigations**

Viral infection is the most common aetiology of infective MC, which remains a complex and challenging diagnosis in cardiology. Recent consensus guidelines recommend diagnosis should be based on clinical presentation and the presence of ECG abnormalities accompanied by biomarkers of myocardial inflammation and/or non-invasive evidence of abnormalities in cardiac structure and/or function [3,205]. Although in the present meta-analysis clinical signs and symptoms of viral CM could not be pooled because insufficient numerical data was provided in the individual studies, common clinical presentation mentioned in more than two studies were fever, shortness of breath, chest pain, palpitations (arrhythmias), pre-syncope or syncope (atrioventricular block), arrhythmia and HF. These signs and symptoms of VCM are consistent with those reported in previous studies although HF, chest pain and arrhythmias have been cited as the most common reason for hospital visitation [205-207]. Most of the enrolled patients in the individual studies had persistence symptoms for more than six months suggesting worsening cardiac function and the likelihood to benefit from immunosuppression. These symptoms were typical of cardiac dysfunction while symptoms of the underlying viral disease or infection were not described in the individual studies. In addition to clinical presentation, common ECG abnormalities in the included studies were T-wave inversion, ST-segment elevation, ST-segment depression, PR depression, and pathologic Q waves. However, ECG abnormalities have been described previously as non-specific to VCM patients since they may mimic other cardiac disorders such as acute myocardial infarction or pericarditis [260]. Clinical presentation and ECG abnormalities are useful for raising clinical suspicion for viral MC and CM, while EMB is the most common test for confirming diagnosis as well as patient selection in almost all the included studies.

Consistent with literature on MC, standardized histopathological description of biopsy sample was used to detect myocardial inflammation associated with necrosis in the absence of ischemia in MC patients [260]. However, histopathology alone has been found to be inadequate to detect the presence of active MC. It is too narrow due to limited variable interpretation, lacks clinical prognostic value, and has poor diagnostic sensitivity and specificity [261]. To improve histological diagnosis of viral MC, additional virological...
and immunological evaluation of myocardial tissues have been recommended using immunohistochemical and PCR techniques, which allow the identification and quantification of inflammatory cells and viral infection markers [261]. Although EMB has been the gold standard for confirmatory diagnosis of infective MC and DCM for long, evidence is emerging that cardiac MRI is an important tool for non-invasive evaluation of patients suspected with MC [220,262,263]. In the diagnosis of VCM, cardiac MRI is used to evaluate functional and morphological abnormalities as well as tissue pathology as a feature of myocardial inflammation. With a lack of consensus on EMB, a recent AHA consensus statement recommends that EMB should be reserved for patients who are likely to have specific myocardial disorders with unique prognoses and specific treatment recommendations [264].

Clinical management

In the present systematic review and meta-analysis, pooled analysis of five studies (N = 406) reveal statistical evidence of beneficial uses of immunosuppressive therapy in addition to standard HF therapy in improving LV systolic function and cardiac hemodynamics (reduction of LV volumes and dimensions). Immunosuppressive therapy also revealed a trend towards reduction in death, and HF hospitalization and/or heart transplantation. Since these benefits are only likely to occur in a sub-group of VMC patients, it underscores the importance of diagnostic methods in the selection of patients who will benefit from treatment. These patients include those with biopsy-proven virus free myocardium in the presence or absence of myocardial inflammation, echocardiographic evidence of depressed systolic function (LVEF ≤45%), and refractory HF symptoms greater than six months despite optimal medical therapy for HF. The importance of patient selection emerged from previous four meta-analyses in which the included studies enrolled patients without evidence of biopsy-proven virus negative myocardium and with HF symptoms less than six months [144-147]. In this meta-analysis, studies reported no evidence of immunosuppressive therapy improving hemodynamics and cardiac function relative to conventional HF therapy or placebo.

The evidence of therapeutic benefits of immunosuppressive therapy is consistent with findings of animal models and proposed tri-phasic pathogenic mechanisms of VMC. The model proposes that VMC begins with an acute phase of viral infection and replication leading to direct viral damage to the myocardium followed by the phase of immune-mediated response to viral infection and its damaging effect on the myocardium due to molecular mimicry and the final phase of cardiac remodelling [55-61]. Immunosuppressive therapy targets the second phase of immune-mediated myocardial damage by suppressing immune response. Patients with biopsy-proven virus free myocardium benefit from immunosuppression because after the completion of the virus-killing phase, the action of autoantibodies on the cardiomyocytes may persist through molecular mimicry in which immunosuppressive drugs reduce cardiomyocyte destruction and prevent its progression to VMC [152,153]. Thus, timing of immunosuppressive therapy is critical because its administration during viral infection and replication phase would suppress the host immune response with deleterious effect on cardiac function. While some studies suggest a positive trend towards immunomodulation and immunoadsorption improving cardiac function in VCM patients in the present analysis, there was no sufficient data to perform a pooled analysis and determine therapeutic value of VCM [152,186,234,235].

Limitations

Despite the present findings supporting the use of immunosuppressive therapy in a sub-group of VMC patients, a few limitations in this meta-analysis should be considered. Most of the data on the use of immunosuppressive therapy have been gathered from animal models or autopsy analysis and extrapolated to the general population while individual large-scale randomized clinical trials are difficult to conduct. This has resulted in the current small sample sizes of the included studies, and heterogeneity in terms of diagnosis, methodology, treatment protocols and outcomes measures. Studies with larger samples are needed to enhance the statistical power detect significant differences in treatment effect for individual studies. The criteria for patient selection into trials is not clearly defined. Most of the patients selected had cardiac symptoms >6 months and biopsy-proven virus free myocardium and thus the findings cannot be applied to all patients with viral infection of the myocardium. Viral MC of DCM is a disease difficult to diagnose at initial presentation because its clinical presentation is protein and with a wide spectrum ranging from asymptomatic phase to acute cardiovascular collapse requiring mechanical support. Moreover, clinical and histological features may overlap with that of inflammatory cardiomyopathy [3]. Upregulated HLA expression in the myocardium is a promising criterion to identify patients who would benefit from immunosuppressive therapy but used by only one study [142].

Clinical implications

The current findings have important clinical implications. Although the findings support the use of immunosuppression, it is based on small-scale individual studies with short-term outcomes that has prevented broad application of its benefits to clinical settings. Small-scale trials might lack the statistical power to detect significant differences in important clinical end-points such as recurrent heart failure, the need for ventricular assist devices, heart transplantation or death. While larger trials with carefully selected patients are needed to confirm the benefits of immunosuppression, its use in a larger population has the potential to cause a measurable increase in immunosuppression-related side effects, infections and possibly malignancies [265]. Larger trials should also have longer follow-up periods to enable prospective evaluations since short-term benefits such as in LV systolic function (LVEF) may not correlate with long-term risk of death or heart transplantation in the subset of VCM patients who are likely to benefit from immunosuppression. Although the use of cellular HLA antigen or adhesion molecule are promising to identify VMC patients who might benefit from immunosuppression, there is no sufficient evidence to support their use in clinical setting. Despite the clinical benefits of immunosuppression based on biopsy evidence of virus negative myocardium, its use is limited because on a small minority of medical centres that possess the capability to perform endomyocardial biopsy and the expertise in cardiac pathology and viral genome analysis. Finally, the present findings would stimulate research for the effect of other medications targeting the immune mechanisms such as immunoadsorption in the prevention of immune-mediate myocardial damage in VMC patients during the chronic phase of the disease.

Conclusion

Viral cardiomyopathy (VCM) is a myocardial disease due to viral persistence in a dilated heart in the absence of myocardial inflammation. Its exact epidemiology is unknown due to wide heterogeneity of
causative viruses and periods of epidemic that alter its prevalence and incidence. The main pathogenic mechanisms are viral and immune-mediated damages to the myocardium leading to myocardial remodelling, or damage to the vascular endothelial cells leading to microvascular dysfunction or the degradation of the interstitial matrix causing LV dilatation and dysfunction. Typical manifestation include chest pains, arrhythmia or heart failure. Endomyocardial biopsy remains the diagnostic gold standard but increased risk of complications and the need for expert knowledge limits its widespread use. The criteria for clinical diagnosis is a combination of symptoms, ECG abnormalities and non-invasive imaging evidence of structural/functional dysfunction. The available treatment strategies include HF therapy for the relief of symptoms and antiarrhythmic therapy for the management of ventricular arrhythmias. In addition to HF medication, immunosuppressive therapy in biopsy-proven virus free myocardium with refractory HF symptoms improves cardiac function and hemodynamics. However, the use of immunosuppressive is limited by insufficient supporting evidence and the lack of expertise needed for heart biopsy. Large-scale studies with a long follow-up period and enrolling carefully selected patients would help to determine long-term outcomes of hard clinical endpoints such as death, hospitalization and heart transplantation to encourage broad adoption of immunosuppression in clinical practice.

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