The Diagnostic and Clinical Approach to Pediatric Myocarditis: A Review of the Current Literature

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Abstract

Myocarditis is an inflammatory disease of the myocardium with a broad spectrum of clinical presentations, ranging from mild symptoms to severe heart failure. The course of patients with myocarditis is heterogeneous, varying from partial or full clinical recovery in a few days to advanced low cardiac output syndrome requiring mechanical circulatory support or heart transplantation. Myocarditis is a very heterogeneous disease, especially in the pediatric age group as worldwide disease myocarditis has been defined by the World Health Organization/International Society and Federation of Cardiology as an inflammatory disease of the heart muscle diagnosed by established histological, immunologic, and immunohistological criteria. Pediatric myocarditis remains challenging from the perspectives of diagnosis and management. Multiple etiologies exist, and the majority of cases appear to be related to viral illnesses. Enteroviruses are believed to be the most common cause, although cases related to adenovirus may be more frequent than suspected. The clinical presentation is extremely varied, ranging from asymptomatic to sudden unexpected death. A high index of suspicion is crucial. There is emerging evidence to support investigations such as serum N-terminal B-type natriuretic peptide levels, as well as cardiac magnetic resonance imaging as adjuncts to the clinical diagnosis. In the future, these may reduce the necessity for invasive methods, such as endomyocardial biopsy, which remain the gold standard. Management generally includes supportive care, consisting of cardiac failure medical management, with the potential for mechanical support and cardiac transplantation. Treatments aimed at immunosuppression remain controversial. The paediatrics literature is extremely limited with no conclusive evidence to support or refute these strategies. All these summarised in this article and the listed current literature showed that there is no consensus regarding aetiology, clinical presentation, diagnosis, and management of myocarditis in pediatric patients.

Introduction

Myocarditis, the inflammation of the muscular walls of the heart, remains a diagnostic challenge in the clinical setting because of the variability of presentations in the pediatric population. It has the potential for significant morbidity including diminished cardiac function and cardiac failure, occasionally necessitating aggressive circulatory support [1]. Dilated cardiomyopathy is a significant sequela of myocarditis and is a common indication for cardiac transplantation. Myocarditis is also identified as the cause of sudden unexpected death in young patients. Nevertheless, this condition remains somewhat enigmatic from the perspective of diagnosis, and there exists considerable variation in management practices. This article aims to summarise the current research and emphasise pertinent aspects of myocarditis for the general paediatrician [2].

Definition

In 1995, the World Health Organization created the following definition: "Inflammatory cardiomyopathy is defined by myocarditis in association with cardiac dysfunction. Myocarditis is an

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inflammatory disease of the myocardium and is diagnosed by established histological/immunological, and immunohistological criteria. Idiopathic, autoimmune, and infectious forms of inflammatory cardiomyopathy are recognised'' [3]. Notably, this inflammation occurs in the absence of ischemia.

Epidemiology

The true incidence of myocarditis in the pediatric population is difficult to measure due to the wide variety of presentations and the lack of diagnostic protocols [4]. Over half of all cases of myocarditis occur in patients below the age of 40 years. A post-mortem analysis showed a prevalence of 3.5-5% [5], but the rate of clinically significant cases more closely approximates 0.1-0.6% [6]. Patients of all ages may be affected, but the majority of cases occur in infants and teenagers; more than one-half of all cases are seen in the first year of life [7]. The reason for this unusual bimodal age distribution is currently unclear. By screening electrocardiograms in Japan, the approximate incidence of myocarditis is estimated to be about 7 per 60,000 (0.012%) asymptomatic children [8], [9]. A recent retrospective review reported the prevalence of myocarditis to be 0.5 cases per 10,000 emergency department visits [10]. Children in this study were diagnosed using history, clinical exam, and various supportive investigations. An approximate incidence may lie between 0.15% and 0.6% in the overall population based on postmortem histology [11]. As myocarditis is also associated with sudden cardiac death in young patients, this may further confound estimates of incidence and prevalence [12], [13].

Aetiology

The multiple etiologies of myocarditis are summarised in Table 1 [14]. It is caused primarily by numerous infectious agents, but it may also accompany autoimmune disease, hypersensitivity reactions, and toxins [15]. Infectious exposures, especially viruses, account for the vast majority of pediatric myocarditis; in Canada and the United States, whereas globally the most common cause is Trypanosoma cruzi (Chagas disease) [16]. The majority of paediatric cases are believed to be due to adenoviruses and enteroviruses, such as coxsackieviruses A and B, parvovirus, echovirus, and poliovirus [17], [18]. The relative frequency of cases related to these viruses is variable, and there is much discussion as to which is more common. In the past,

enteroviruses, especially the coxsackieviruses, were considered the most common aetiology. A recent study suggested that adenovirus may be a more significant pathogen than previously recognised [19]. Among patients given a clinical diagnosis of myocarditis, those with positive adenovirus polymerase chain reaction were less likely to have a corresponding histological diagnosis of acute myocarditis compared with the enterovirus group (40% versus 79%) [20]. This suggests that adenovirus is associated with a lesser degree of inflammation in the myocardium. This may suggest a higher prevalence of adenovirus than suspected [21].

A subsequent study reviewed etiologies for biopsy-confirmed myocardial inflammation and found parvovirus B 19 to be the most common, followed by enterovirus, human herpesvirus 6, and then adenovirus [21], [22]. Following the H1N1 Influenza A pandemic, there were case reports of associated myocarditis. Of the 80 confirmed viral infections reported by one group, there were four cases of associated myocarditis, three of which presented with fulminant myocarditis: one patient had a fatal outcome due to acute atrioventricular block, and two required extracorporeal membrane oxygenation support due to severely reduced left ventricular systolic function.[23,24] Extracorporeal membrane oxygenation is implemented in many paediatrics tertiary centres for either respiratory failure or cardiac compromise in cases of H1N1 infection. Further population data are required to clarify the clinical course of H1N1-associated myocarditis [25].

Table 1: Various causes of myocarditis

Aetiology	Examples
Infectious	*Viral:* adenoviruses, echoviruses, enteroviruses (eg, coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza A virus, parvovirus B19 *Bacterial:* chlamydia, Corynebacterium diphtheria, Klebsiella, Salmonella, Legionella, Mycobacterium tuberculosis, mycoplasma, staphylococcus, streptococcus A, Streptococcus pneumonia, Tryponema Pallidum, Haemophilus influenzae *Fungal:* actinomyces, aspergillus, candida, cryptococcus *Helminthic:* Echinococcus granulosus, Trichinella spiralis *Protozoal:* Toxoplasma gondii, Trypanosoma cruzi *Rickettsial:* Coxiella burnetti, Rickettsia typhi *Spirochetal:* Borrelia burgdorferi, leptospira, Treponema pallidum
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematodes, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitivity reactions	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab
Toxic	Amitriptyline, Amphotericin B, Cannabis, Carbon monoxide, Cyclophosphamide, Electric shock, Ethanol, Hymenoptera, Isoniazid, Lead, Lidocaine, Methyldopa, Nonsteroidal anti-inflammation, Phenytoin, Snake or scorpion venom,
Others	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

Pathology and pathophysiology

There are several proposed mechanisms of myocardial injury in viral myocarditis [4], [5], [21]. The

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inflammatory process begins when the body's immune cells (the cells that fight infection) penetrate the heart tissue. These immune cells become activated and produce chemicals that can cause damage to the heart muscle cells. There are thickening and swelling of the heart muscle. All four chambers of the heart may be affected and become enlarged [24], [25]. These include the excessive immune-mediated destruction of the myocardium by infiltrating immune cells targeting the infected cardiomyocytes; autoimmune-mediated destruction of cardiac cells by circulating autoantibodies; and direct virus-induced cardiac myocyte injury. It is proposed that three phases of viral myocarditis exist, beginning with a period of viral replication, followed by acute injury to the myocytes, and subsequent evolution of dilated cardiomyopathy, associated with profound alteration in the extracellular matrix of heart muscle [4], [8], [9], [22].

Mechanism of developing the myocarditis after infection of cardiac endothelial cells or cardiac myocytes by virus leads to direct cellular damage. A subsequent innate and adaptive immune response develops that can evolve into resolution and healing or dilated cardiomyopathy resulting from severe initial injury, persistent inflammation, or persistent viral infection. Adapted from Schultheiss et al., [5] with permission of the publisher.

Damaged muscle cells may heal over time, or there may be cell death followed by scar formation. If this process is extensive and a large portion of the heart is involved, the heart's ability to pump blood is impaired. As a result, the key organs and tissues in the body do not get enough oxygen and nutrients and cannot get rid of waste products. This is often referred to as congestive heart failure. Up to 27% of dilated cardiomyopathy cases in children may be attributable to viral myocarditis [23], [24].

Clinical presentation

Cardiovascular syndromes observed with pediatric myocarditis are sudden death, arrhythmias, chest pain, myocardial infarction, acute heart failure with a dilated cardiomyopathy phenotype.

Sudden death

Sudden death in the pediatric population is commonly associated with myocarditis, and it may be the presenting feature of myocarditis, and in these cases, the diagnosis is often made histologically. It is suggested that some cases may be the result of inflammatory infiltrates that act as arrhythmogenic foci, leading to fatal arrhythmia. Studies of sudden infant death syndrome have linked infection with viruses such as enterovirus, adenovirus, parvovirus B19, and Epstein-Barr virus and myocarditis to sudden infant death syndrome victims [25], [26]. A broad clinic-pathological classification system can be used in which there are four categories of myocarditis in the setting of a viral illness. Myocarditis accounted for ≈ 9% of sudden deaths in young athletes in the United States in whom a confirmed cardiovascular event was documented. Despite the existence of echocardiographic and endomyocardial biopsy criteria for myocarditis and resulting cardiomyopathy, expert opinion currently suggests that the diagnosis of "probable" myocarditis is based on clinical judgement [27].

Arrhythmias

Symptoms such as palpitations and syncope occur in pediatric myocarditis patients even in the absence of heart failure or demonstrable reduction of left ventricular function. Pediatric ventricular arrhythmias in structurally normal hearts and ventricular tachyarrhythmias in athletes have been associated with myocarditis [28], [29]. Myocarditis should always be considered in a child with acquired complete heart block. Lyme carditis and Chagas disease have been associated with complete heart block. Although the majority of children may recover atrioventricular conduction, most patients need implantation of a permanent pacemaker [30], [31], [32].

Chest Pain/Myocardial Infarction

More than 20 years ago, it was recognised in adults and children that myocarditis might mimic myocardial infarction with severe symptomatic chest pain, characteristic ECG findings, and elevation of serum creatinine kinase, in the presence of normal coronary angiograms. Coronary spasm has been observed with this presentation in adults [33], [34]. Parvovirus B19 has been found in the myocardium of such patients, as well as adenovirus and Epstein-Barr virus [35]. In a study of 4436 patients presenting to a pediatric emergency department with chest pain, 24 had a confirmed cardiac origin, of whom four were diagnosed with myocarditis [36]. A recent study of pediatric patients, presenting with myocarditis and a chest pain/myocardial infarction pattern, found that all had elevations of cardiac troponin I (peak range, 6.54–64.59 ng/mL), in the presence of normal values of erythrocyte sedimentation rate and C-reactive protein. Echocardiograms demonstrated a mild reduction in left ventricular function in 57% of the patients, and 5 of 6 patients demonstrated cMRI findings consistent with myocarditis. The prognosis was good with a resolution of cardiac abnormalities within a few weeks, similar to the adult experience [37], [38].

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Acute heart failure with dilated cardiomyopathy phenotype

The classic presentation of myocarditis is the development of symptoms of heart failure with a dilated cardiomyopathy phenotype a few weeks after a history compatible with a viral illness, including fever, myalgias, and respiratory or gastrointestinal symptoms. Myocarditis accounts for 30% to 35% of children with dilated cardiomyopathy phenotypes in the Australian and North American pediatric cardiomyopathy registries and for 22% of new-onset left ventricular dysfunction in the United Kingdom [38, [39], [40].

Fulminant myocarditis is a distinct subset of acute myocarditis characterized by heart failure with severe hemodynamic compromise requiring inotropic or mechanical circulatory support and at least 2 of the following criteria: fever, distinct onset of heart failure symptoms within a 1- to 2-day period, and a history consistent with viral illness within the 2 weeks before hospitalization. Fulminant myocarditis is associated with symptoms of significant left ventricular dysfunction and unexpected cardiac failure within 2–3 weeks of the onset of viral infection [40], [41]. Fulminant myocarditis has been described in children with mortalities varying from 48.4% in Japan to 9% in France. Despite the severe presentation, outcomes are substantially better than in adults with acute myocarditis. Acute myocarditis presenting with severe heart failure, arrhythmias, and lack of responsiveness to supportive care after 1 to 2 weeks leads to concern for giant cell myocarditis, which can be diagnosed by biopsy and has a grim prognosis, although is responsive to immunosuppression [42].

Acute myocarditis in children has been associated with a good prognosis with a good chance for ultimate recovery of left ventricular dysfunction [16], [17]. Within the North American Pediatric Cardiomyopathy Registry (PCMR), 372 myocarditis patients diagnosed by biopsy (n = 119) or clinical criteria (n = 253) were compared with 1123 patients diagnosed with idiopathic dilated cardiomyopathy. Outcomes were similar in the biopsy and clinically diagnosed myocarditis patients and substantially better than in children diagnosed with idiopathic dilated cardiomyopathy. These results are similar to an estimated 58% spontaneous recovery in acute adult myocarditis gleaned from an adult meta-analysis [43].

"Subacute myocarditis" can be described as moderate left ventricular dysfunction and has less distinct clinical features of the disease.

"Chronic active myocarditis" is associated with moderate left ventricular dysfunction, indistinct symptoms, and endomyocardial biopsy reveals ongoing inflammation, myocardial damage, and active scar tissue.

"Chronic persistent myocarditis" is described in the setting of normal left ventricular function and palpitations or atypical chest pain, with persistent inflammation on biopsy [44].

Myocarditis in children is associated with a high rate of congestive heart failure, hospitalisation, intensive care unit stay, and use of inotropic support at the time of diagnosis compared with children with idiopathic dilated cardiomyopathy. A recent study of hospitalised patients in the United States found that nearly half of the patients required inotropic support, 37.5% required mechanical ventilation, and 7.4% required extracorporeal membrane oxygenator (ECMO) support [23], [45].

Diagnosis

History and physical examination

The diagnosis of pediatric myocarditis is especially challenging because of the variable clinical presentation, ranging from asymptomatic patients with only subtle findings on an electrocardiogram to fulminant cardiac failure and sudden death. Diagnosis remains largely based on clinical judgement, supported by ancillary tests; therefore, a high index of suspicion is necessary. Clinical features are often those of congestive cardiac failure and myocarditis is identified as the most common cause of new-onset cardiac failure in previously well children [22], [46]. Even patients with mild symptoms are at risk of deterioration, and therefore early diagnosis is important in establishing appropriate monitoring and supportive care.

The majority of patients present with a resting tachycardia, but other cardiac-specific signs such as pallor, hypotension, oedema, and hepatomegaly occur in only a minority of cases. Chest pain, syncope, and palpitations may also be presenting complaints. Fever may or may not be present. There are several paediatric studies that have examined the most common signs and symptoms of patients with myocarditis. Shortness of breath, respiratory distress, or an abnormal respiratory exam were commonly observed [22], [47]. In two studies, 84% of patients required more than one visit to a physician within 14 days before the diagnosis of myocarditis or dilated cardiomyopathy was made [23].

Children were often given an initial diagnosis of asthma or pneumonia [5]. Resting tachycardia is also an important subtle feature, and although this is not always a consistent finding, it may be the only finding of mild disease [5], [48]. Isolated vomiting is observed, and this may be due to gut ischaemia secondary-to-low cardiac output. Isolated gastrointestinal symptoms of anorexia, abdominal pain, and vomiting may also occur. Hepatomegaly is a

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common feature on physical exam and may present as non-specific abdominal pain [5], [23]. In contrast to adults with myocarditis, chest pain is seldom reported in younger children though it may be a more common feature in adolescents. A case series of several teenage patients diagnosed with myocarditis described symptoms of severe chest pain, in combination with elevated cardiac troponin-I, ST-segment, and T-wave changes [24], [48].

Investigations

Despite many diagnostic modalities, suspicion of myocarditis is mainly based on clinical criteria. Diagnostic workup should include baseline investigations listed in Table 3. Abnormal troponin levels may support a diagnosis of myocarditis, but there are limited data in the current pediatric literature [29], [49]. An elevated creatine kinase level may also be observed in myocarditis, although it is a non-specific marker.

It has been suggested that, in comparison with creatine kinase, cardiac troponin-T may provide better sensitivity for detecting micronecrosis in myocarditis because of a proportionally higher and longer-lasting elevation of serum levels [30], [50]. In the Myocarditis Treatment Trial, elevations of cardiac troponin I occurred more frequently than did elevations of creatine kinase muscle and brain subunits in patients with biopsy-proven myocarditis [31], [51]. There was one pediatric study that illustrated a cut-off point for a cardiac troponin T level of 0.052 nanograms per millilitre for diagnosing acute myocarditis with a sensitivity of 71% and specificity of 86%, although there was no correlation between cardiac troponin T level and ejection fraction [32], [52].

Use of the N-terminal segment of the B-type natriuretic peptide prohormone levels may be helpful in the setting of myocarditis, especially concerning recovery. In one study, elevated N-terminal B-type natriuretic peptide levels correlated well with clinical status and echocardiographic findings in patients with dilated cardiomyopathy or myocarditis [33], [53], [54]. N-terminal B-type natriuretic peptide levels had 78% sensitivity and 100% specificity for the diagnosis of persistent left ventricular dysfunction. Patients who recovered had N-terminal B-type natriuretic peptide levels that were within normal limits [55].

Chest X-ray findings often include cardiomegaly and may demonstrate pulmonary oedema, infiltrates, or pleural effusions [6], [34].

Electrocardiogram ECGs are virtually always abnormal in children with myocarditis, found in over 93% of patients but a normal ECG does not rule out the possibility of the disease [23], [56]. ECG abnormalities, however, are widely variable, and there is not one specific abnormality that occurs with enough frequency to be a specific marker. The most common abnormalities include sinus tachycardia, criteria for ventricular hypertrophy, ST segment, and T-wave abnormalities. Premature contractions and a wide variety of tachyarrhythmias and bradyarrhythmias occur in myocarditis, including complete atrioventricular block, atrial and ventricular delays and prolongation of QT intervals may also occur. The combination of an electrocardiogram with chest X-ray in the setting of possible myocarditis has very good sensitivity for the diagnosis [4], [13], [57].

Echocardiographic findings may include increased ventricular end-systolic or diastolic dimensions, reduced shortening or ejection fractions, atrioventricular valve regurgitation, and regional wall motion abnormalities [36]. Echocardiography is also important to rule out coronary abnormalities as a cause of depressed myocardial function. Abnormal right ventricular function on echo may be associated with an increased likelihood of adverse outcomes including cardiac transplantation or death [37]. Other methods of non-invasive imaging are being investigated in the setting of myocarditis.

Nuclear medicine techniques have not been used widely in paediatrics, in part due to concerns of excessive radiation exposure for children [38].

Cardiovascular magnetic resonance imaging is a widely accepted tool to assess myocarditis. This technique provides a detailed not only functional and morphological assessment of the heart, but also reliable visualisation of tissue markers of myocarditis including oedema, inflammation, and fibrosis [41], [43]. Previously, oedema could not be well imaged; however, cardiac magnetic resonance is now able to visualise myocardial oedema without using radiation or contrast agents. Currently, cardiac magnetic resonance may be considered the single best non-invasive imaging study for this indication, and standardised protocols for cardiac magnetic resonance imaging of myocarditis are available [42]. In acute myocarditis, cardiac magnetic resonance assessment of myocardial oedema is performed using T2-weighted short TI inversion recovery imaging in which regions of myocardial oedema appear bright, whereas fat and blood signals are suppressed.

The sensitivity and specificity of T1-weighted images in patients with suspected chronic myocarditis were 62% and 86%, respectively, using immunohistological methods as the gold standard [39]. Similar to myocardial oedema, early enhancement normalises approximately 4 weeks after the clinical presentation and therefore may be used as a marker of the acuity of myocardial injury [23]. In a small proportion of patients, the early enhancement may persist and is correlated to reduced cardiac function. It is not currently known whether persistently elevated early enhancement truly reflects an ongoing

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viral infection. The cardiac magnetic resonance technique of gadolinium late enhancement allows visualisation of myocardial necrosis and fibrosis associated with myocarditis.[58] Gadolinium accumulates in regions of fibrosis, leading to increased signal intensity in late enhancement images. In the setting of myocarditis, the pattern of myocardial fibrosis varies considerably but typically involves patchy focal fibrosis of the sub-epicardium or mid-myocardial wall, rarely extending to the sub-endocardium [41], [43]. The presence of myocardial fibrosis detected by cardiac magnetic resonance late enhancement is more common in males and younger patients, and the pattern of myocardial injury sustained in young patients tends to be more regional and more severe, with a higher incidence of irreversible myocardial scarring [28]. This pattern of myocardial injury may explain why younger patients are at risk of adverse cardiac outcomes — the presence of gadolinium late enhancement 4 weeks after the acute presentation is also correlated with reduced left ventricular ejection fraction and clinical symptomatology at 30-month follow-up [58].

To standardise cardiac magnetic resonance imaging to diagnose myocarditis, the International Consensus Group on Cardiovascular Magnetic Resonance created new criteria, known as the "Lake Louise Criteria". These recommendations describe indications for cardiac magnetic resonance in patients with suspected myocarditis, cardiac magnetic resonance protocol standards, terminology for reporting cardiac magnetic resonance findings, and diagnostic cardiac magnetic resonance criteria for myocarditis. These guidelines report that the greatest balance of diagnostic sensitivity and specificity for acute myocarditis is achieved with the presence of any two or more of the following three criteria: myocardial oedema (T2 short TI inversion recovery), hyperaemia/capillary leak (early enhancement), or myocardial fibrosis (late gadolinium enhancement) [59], [60].

The gold standard for the diagnosis of myocarditis remains endomyocardial biopsy; however, this approach has significant limitations [26]. According to the Dallas Criteria, endomyocardial specimens are considered diagnostic of active myocarditis, if routine light microscopy reveals infiltrating lymphocytes and myocytolysis [26]. Borderline or ongoing myocarditis is defined as lymphocytic infiltration in the absence of myocytolysis. A biopsy is considered negative, if both lymphocytic infiltration and myocytolysis are absent [27], [61].

A potential reason to proceed with biopsy is that the presence of immune complexes and complement deposits supports an immune-mediated process; therefore, the management may differ from that of the case of viral infection. For example, immune suppression is not indicated in cardiomyopathy but may be worthwhile in viral myocarditis. A biopsy may be useful in the setting of

eosinophilic infiltrates, which could suggest a hypersensitivity response to an exogenous agent. In this case, once the histology is confirmed, the offending agent can be removed, and the clinical picture may improve. A significant limitation of cardiac biopsy is that myocarditis affects the myocardium in a patchy fashion, and therefore negative biopsy may not exclude disease [62], [63].

There remains controversy as to whether or not to proceed with biopsy, especially since biopsy can be associated with arrhythmia and perforation of cardiac tissue. Pediatric literature also suggests that the highest rate of complication occurs in patients being evaluated for myocarditis, as well as those requiring inotropic support [49], [63]. Despite the overall complication rate being relatively low (1-6%), with mortality between 0.0% and 0.4%, risk-benefit analysis occurs on a case-by-case basis [49], [64].

Table 2: Diagnostic classification for patients with myocarditis

Criteria	Pathological Confirmation	ECG or Imaging
Possible subclinical acute myocarditis In the clinical context of possible myocardial injury without cardiovascular symptoms but with at least 1 of the following Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed
Probable acute myocarditis In the clinical context of possible myocardial injury with cardiovascular symptoms and at least 1 of the following: Biomarkers of cardiac injury raised ECG findings suggestive of cardiac injury Abnormal cardiac function on echocardiogram or cardiac MRI	Absent	Needed
Definite myocarditis Histological or immunohistological	Needed	Not needed

Treatment

Despite improved understanding of the pathogenesis of myocarditis, treatment strategies remain controversial, and the general approach is supportive. The stabilisation of children who present with hemodynamic compromise and early involvement of pediatric cardiology specialists are crucial. Treatment of congestive cardiac failure may include diuretics, afterload reduction, inotropic support, anticoagulation, arrhythmia management, and ventilatory support [64], [65].

Aggressive administration of intravenous fluids initially may exacerbate cardiac failure. Transfusions of packed red blood cells may be required to optimise oxygen carrying capacity.

The use of inotropes such as dopamine, dobutamine, and milrinone may be necessary. Afterload reduction, if it can be tolerated, with

phosphodiesterase inhibitors such as milrinone can be extremely useful. It is also suggested that the early introduction of angiotensin-converting enzyme inhibitors, as well as beta-blockers, once the acute decompensatory phase has begun to resolve, may be beneficial. These medications may help prevent the remodelling that evolves to dilated cardiomyopathy as well as relieving vasospasm to some degree [17], [18]. In pediatric patients, carvedilol was suggested in this regard but has not been studied extensively [67]. Anticoagulation may be recommended if the ejection fraction is severely decreased or in the setting of atrial arrhythmias [55]. Some patients may require ventilatory support as a means of reducing cardiac demand. Ventilation and oxygenation may be best managed with continuous positive airway pressure or other non-invasive methods, for several reasons. Increased intrathoracic pressure via nasal or mask continuous positive airway pressure may help to reduce left ventricular afterload by reducing transmural myocardial wall tension, without causing the hypotension associated with pharmacologic afterload reduction. Intubation medications can cause hypotension and acute cardiovascular collapse; therefore, continuous positive airway pressure may also circumvent this and is an excellent adjunctive therapy for decompensated cardiac failure [43], [55]. Those with more severe cases of myocarditis may require circulatory support in the form of extracorporeal membrane oxygenation or ventricular assist devices.

Immunomodulation, immunosuppression and antiviral therapy

Animal studies have suggested that myocarditis has a 3-phased course [31]. Phase 1 involves initial direct myocardial injury from the actively replicating virus or the innate immunological response from infection of cardiac myocytes, fibroblast, or endothelial cells. Phase 2 is marked by activation of antigen-specific immunity involving T cells, B cells, and antibody production. Various chemokines are present that may contain the inflammatory response but extend tissue injury. Development of autoantibodies and persistent T-cell activation can be induced by antigens intrinsic to the myocardium that cross-react with viral peptides (molecular mimicry). Ultimate outcomes may vary. Negative immune modulation may occur rapidly after the elimination of the infectious pathogens, leading to a cessation of the inflammatory response with a complete recovery or little long-term myocardial damage. However, phase 3 may occur in which acute myocarditis leads to a chronic dilated cardiomyopathy. This may result from severe myocardial injury caused by the acute event; an ongoing inflammatory,

autoimmune process that may occur without the persistent presence of virus in the myocardium (inflammatory dilated cardiomyopathy); or ongoing direct injury from virus with or without a persistent myocardial inflammatory response (viral heart disease) [7], [8], [66], [67].

An area of significant controversy involves the use of immune suppression and immune modulators in the context of myocarditis. There are large-scale adult studies concerning immune suppression, and overall the data have shown some limited, short-term response to these therapies. In two large adult prospective studies, immunosuppression including prednisone with or without azathioprine or cyclosporine was used [68], [69]. With prednisone alone, there was a modest improvement in left ventricular function in patients with evidence of inflammation on biopsy; however, this improvement was not sustained. The Myocarditis Treatment Trial found no significant improvement in function and no difference in survival when compared with controls [2], [70].

Despite the existence also of a handful of uncontrolled studies that showed benefit with various immunosuppressive regimes, some meta-analyses of adult studies did not show a significant beneficial effect of immunosuppression [6], [71]. It is always difficult to extrapolate the findings of adult studies to the pediatric population. Pediatric studies are limited, and there are no randomised controlled trials. Many used prednisolone and did find some benefit, though not always statistically significant, by adding a second agent. In one trial, patients were stratified into either standard treatment, or given one of three immunosuppressive therapies, prednisolone, prednisolone and azathioprine, or prednisolone and cyclosporin A [70]. The groups receiving immunosuppressive treatment with a second agent, in addition to the prednisolone, showed improved hemodynamic parameters, as well as histological improvement in inflammation [72]. Some small case series suggested some clinical benefit to immunosuppressive treatment, again using corticosteroids with an additional agent; however, most were small, uncontrolled studies [22] A meta-analysis of pediatric studies between 1984 and 2003 systematically reviewed the impact of immunosuppressive therapy in children with myocarditis and overall found no consistent benefit [73. This included nine pediatric studies, all of which were small and very heterogeneous in design. Many of the studies were retrospective and uncontrolled, introducing significant bias.

Intravenous immunoglobulin was also examined as a potential immunomodulating therapy to decrease inflammation potentially. Despite some studies observing a trend towards improved cardiac status following treatment, there are no randomised controlled trials using intravenous immune globulin in children with myocarditis. A few authors conducted a

comprehensive multi-database search including patients of all ages with myocarditis treated with intravenous immune globulin. They concluded that if there is evidence that ongoing, active infection may be causing persistent cardiac dysfunction, intravenous immune globulin may be helpful [74]. Even if post infectious inflammation is the most likely aetiology, intravenous immune globulin may still be beneficial by preventing the formation of cytokines [16], [17]. There is one multi-centre adult randomised controlled trial using intravenous immune globulin [75]. They found no significant difference in rates of survival, cardiac transplantation, use of ventricular assist devices, improvement in ventricular function, or functional capacity at 1 year of follow-up. A Cochrane review of intravenous immune globulin in dilated cardiomyopathy or myocarditis showed no benefit in adults; however, some case reports and case series suggested that adults treated with intravenous immune globulin did exhibit improved cardiac function [15], [16], [28], [76]. Some case reports and series in children have shown improved ventricular function and clinical improvement after high-dose intravenous immune globulin, however with small numbers.[77] Overall, it was felt that the validity of many of these studies was compromised due to the lack of control groups. There was one case report of coxsackievirus A19 myocarditis in which intravenous immune globulin was not effective, and another case series found no additional benefit by adding intravenous immune globulin to steroid treatment [78].

Studies using immunosuppressive or immunomodulating treatments, therefore, were difficult to translate into an effective, routine therapy for children or adults with myocarditis. Many patients with myocarditis have spontaneous improvement. It is difficult to know if the observed improvement after treatment with immunosuppression or intravenous immune globulin is attributable to treatment versus the natural course of the disease. Potentially, some aetiologic types of myocarditis respond differently, and certain histologic characteristics may make specific patients better responders than others [9], [11], [79]. Further studies are needed to determine the possible utility of immunosuppressive or immunomodulating therapy.

Therapy for advanced heart failure/cardiogenic shock in pediatric myocarditis

Acute pediatric myocarditis is commonly associated with severe, progressive heart failure. The majority of patients receives care in an intensive care unit at presentation and is treated with intravenous inotropes [80]. Mechanical circulatory support is frequently required when pharmacological therapy is ineffective, as reflected in evidence of elevated blood lactate levels and evidence of end-organ dysfunction [32]. Most commonly, ECMO support is used. ECMO is currently used in ≈ 20% of American children hospitalised with myocarditis [81]. Some single-centre studies have reported hospital discharge rates of ≈ 80% in pediatric myocarditis requiring ECMO support, with ≈ 60% of the patients experiencing myocardial recovery. Multicenter data from the Extracorporeal Life Support Organization (ELSO) registry demonstrated a lower hospital discharge rate of 61% in 10 years from 1995-2006 [51], [82].

ECMO provides biventricular circulatory support but does not decompress the left ventricle. Patients placed on ECMO will initially demonstrate a stunned, left ventricle with no effective ejection, which can lead to a need for decompression of the left ventricle via a left-sided vent or atrial septostomy in as many as 30% of cases–to avoid pulmonary venous hypertension and pulmonary haemorrhage [83]. Evidence of improved left ventricular ejection usually appears less than a week after the initiation of ECMO. Although ECMO can provide effective short-term (< 2 weeks) support, survival was < 50% in myocarditis patients requiring > 2 weeks of support in the ELSO registry. Factors associated with death on ECMO have included the presence of arrhythmia on support, the need for dialysis, and higher stages of end-organ hypoperfusion, as reflected in serum lactate, creatinine, and aspartate aminotransferase levels [84], [85]. In 1 centre's experience, the absence of the virus in the myocardium or evidence of myocardial inflammation was associated with a greater chance for recovery [86].

Ventricular assist devices (VADs) have revolutionised the care of adults with advanced heart failure. VAD support, usually in the form of left ventricular assist devices as opposed to biventricular assist device support, is being increasingly–used in pediatric myocarditis [78], [87]. Continuous-flow VADs, used in adults, are limited to use in older children and adolescents, although the Heartware device has been used in children as small as 0.8 m^2. Initial experience with the use of these devices in the pediatric population is favourable, with low mortality and morbidity rates, similar to the adult experience [88], [89].

The primary use of pediatric VADs is as a bridge to heart transplantation. In the Berlin EXCOR trial, the mortality in patients on the device was 8%, and 87.5% of patients placed on the device received transplantations. This experience is similar to the recent experience in pediatric patients using adult continuous-flow VADs [90]. The overall mortality rate in patients on the device in the United States during the period of the trial was 26% with a transplantation rate of 67%, reflecting the ability of centres to use the Berlin EXCOR on a compassionate-use basis during the conduct of the trial [91], [92]. Lower patient weight (especially < 5 kg), elevated serum bilirubin, lower

estimated glomerular filtration rate, and use of biventricular assist device support was associated with mortality with the device. These encouraging outcome results were tempered by high rates of neurological adverse events (29%, primarily thromboembolic stroke), major bleeding (44%), and major infection (44%) [93].

Outcomes and prognosis

As described, it is difficult to estimate the true incidence and prevalence of myocarditis because of the broad spectrum of symptoms. It is said that the prognosis for children with viral myocarditis tends to be more positive than the outcomes with dilated cardiomyopathy [2], [88]. Survival rates for paediatric patients with myocarditis can be as high as 93% [81]. However, a large, multi-centre study including all age groups showed that there was significant mortality in neonates and infants (33-45% survival, 23-32% improvement) with better outcomes in children between 1 and 18 years of age (78-80% survival, 46-67% improvement) [18].

A study of 28 children with a diagnosis of myocarditis also observed that only 17 survived to hospital discharge with variable degrees of improved heart function, whereas the remaining 11 patients developed intractable cardiac failure leading to cardiac transplant listing (seven cases) or death (four cases) [45]. Predictors of a poor outcome were found to be ejection fraction less than 30%, shortening fraction less than 15%, left ventricular dilatation, and moderate-to-severe mitral valve regurgitation.98 The authors of several case series involving children requiring mechanical support for myocarditis have reported survival rates of 67-83% [67], [78], [79]. An updated review of the extracorporeal membrane oxygenation registry revealed a survival rate of 61% for children supported through acute myocarditis [91]. This is comparable to, and perhaps better than, survival rates of children supported with extracorporeal membrane oxygenation after repair or palliation of congenital cardiac disease, in which survival rates range between 37% and 42% [86]. Hetzer reported that of 21 children supported with the Berlin Heart Excor device for myocarditis or cardiomyopathy, 90% survived to hospital discharge [87]. Collective experience with ventricular assist devices in this setting, however, is quite limited. The prognosis in biopsy-proven myocarditis may depend on the severity of symptoms, histologic classification, and biomarkers. Acute fulminant myocarditis is associated with better overall survival [56], [93]. Giant cell myocarditis, although rare, is associated with especially poor outcomes and a reported median duration of survival, if untreated, of 5.5 months [81]. It also carries an 89% rate of death or transplant.

Myocarditis may account for nearly half of all children with dilated cardiomyopathy [84], [91]. The outcomes for patients with acute viral myocarditis are much better than cases with established dilated cardiomyopathy [92]. For this reason, a high index of suspicion for the disease, and early effective supportive care are crucial. Myocarditis remains a relatively common indication for transplant listing.

Overall, 1-8% of patients with acute myocarditis eventually go on to transplant [25]. Owing to the potential for recovery, even with severe disease at presentation, patients are not typically listed for cardiac transplant unless a recovery is considered extremely unlikely despite reasonable management and a period of observation.

Conclusions

Acute myocarditis comprises a wide clinical spectrum including the asymptomatic patient with subclinical myocardial dysfunction to severe cardiac failure or sudden cardiac death. In paediatrics, the symptoms and signs can mimic many other common diseases and a high index of clinical suspicion is imperative. Treatment of myocarditis remains supportive and should be initiated even before solidifying the diagnosis. Biopsy remains the gold standard for diagnosis; however, it has significant limitations. Cardiac magnetic resonance imaging has become a widely accepted non-invasive imaging modality for myocarditis and standardized protocols are now available for myocarditis. There exist controversial data and no consensus with respect to immunosuppressive or immunomodulating therapy for myocarditis. Similarly, there is no foundation of evidence to indicate a routine treatment strategy other than standard cardiac failure management for these patients. Most patients with myocarditis have spontaneous improvement in their cardiac function and symptoms; however, there remains significant morbidity and mortality associated with this condition. Additional studies are a necessity to clarify the most appropriate management options in pediatrics to improve outcomes.

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