Circulation

Diagnosis and Management of Myocarditis in Children

A Scientific Statement From the American Heart Association

Endorsed by the Myocarditis Foundation

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ABSTRACT: Myocarditis remains a clinical challenge in pediatrics. Originally, it was recognized at autopsy before the application of endomyocardial biopsy, which led to a histopathology-based diagnosis such as in the Dallas criteria. Given the invasive and low-sensitivity nature of endomyocardial biopsy, its diagnostic focus shifted to a reliance on clinical suspicion. With the advances of cardiac magnetic resonance, an examination of the whole heart in vivo has gained acceptance in the pursuit of a diagnosis of myocarditis. The presentation may vary from minimal symptoms to heart failure, life-threatening arrhythmias, or cardiogenic shock. Outcomes span full resolution to chronic heart failure and the need for heart transplantation with inadequate clues to predict the disease trajectory. The American Heart Association commissioned this writing group to explore the current knowledge and management within the field of pediatric myocarditis. This statement highlights advances in our understanding of the immunopathogenesis, new and shifting dominant pathogeneses, modern laboratory testing, and use of mechanical circulatory support, with a special emphasis on innovations in cardiac magnetic resonance imaging. Despite these strides forward, we struggle without a universally accepted definition of myocarditis, which impedes progress in disease-targeted therapy.

Key Words: AHA Scientific Statements ■ heart disease ■ immune system diseases ■ infections ■ inflammation ■ myocarditis ■ pediatrics ■ ventricular dysfunction

Myocarditis in children challenges the practitioner on every front, from the appropriate diagnostic workup to the aggressiveness of intervention and the type and extent of follow-up after recovery. Many patients have spontaneous recovery, and just as many will sustain irreversible myocardial injury, sometimes pressing the practitioner to make medical decisions without a confirmed diagnosis or decisions on therapy that are not evidence based. Myocarditis in children shares features with that in adults, such that a supplemental section on the adult perspective highlights some of these major similarities and differences. However, given its distinct characteristics in children and the potential impact on their lifelong health, the American Heart Association commissioned this statement to provide guidance on its management specific to the pediatric population.

DEFINING MYOCARDITIS

Efforts to define myocarditis have evolved. Initially, pathologic evidence of an inflammatory cardiomyopathy was required. Currently, biopsy rates are declining as practitioners increasingly rely on cardiac magnetic resonance (CMR) imaging and incorporation of clinical and laboratory criteria.[1,2] Guided by review of the literature, expert opinion, and modern practice patterns, this statement recognizes 4 strata that can confirm the diagnosis: (1) biopsy proven, (2) CMR-confirmed clinically suspected,
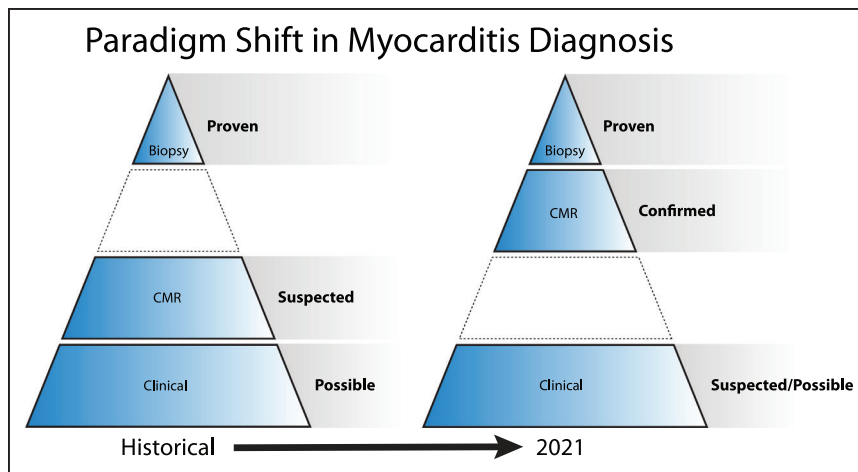
Figure 1. Four strata of certainty in the diagnosis of myocarditis include biopsy proven, clinically suspected confirmed by cardiac magnetic resonance (CMR), clinically suspected, and possible myocarditis. The shift in diagnosis acknowledges advancements in CMR and improvement in identifying a constellation of clinical findings supportive of myocarditis. Dotted empty boxes illustrate gaps in the tiers of diagnostic certainty and opportunities for further advancement.

(3) clinically suspected, and (4) possible myocarditis (Figure 1). The paradigm shift in diagnosis acknowledges advancements in CMR but needs and deserves further study of its accuracy. A positive biopsy proves myocarditis, but like CMR, a negative result does not necessarily rule it out. Clinically suspected myocarditis represents a constellation of findings supportive of the diagnosis of myocarditis when biopsy and CMR cannot be performed or despite their negative results. To date, there are no definitive criteria using clinical features alone to confirm the diagnosis of myocarditis or to differentiate clinical suspicion from possible myocarditis. Nevertheless, this statement discusses clinical and laboratory features that may upgrade a case from possible to clinically suspected myocarditis in the current era. Accuracy (specificity and sensitivity) of most of the testing in a properly studied population is lacking. Hence, proof or confirmation by biopsy or CMR is encouraged, and patient safety and CMR capabilities should also be taken into consideration.

IMMUNOPATHOGENESIS

Innate Immune Response

The pathogenesis of myocarditis depends on the specific pathogen. A virus can gain entry to cardiomyocytes, endothelial cells, and stromal cells through the use of virus-specific receptors. Coxsackie-adenovirus receptor is highly expressed in the heart, with higher expression in younger rat hearts. The death of these infected cells activates innate immune response through receptors recognizing specific pathogen-associated molecular patterns or pattern recognition receptors such as Toll-like receptors. Acute inflammatory mediators such as TNFα (tumor necrosis factor-α), IL-1β (interleukin-1β), IL-6 (interleukin-6), and nitric oxide are released and activate innate immune cells that reside in the heart. The inflammatory mediators can further facilitate activation of stroma cells. Cardiac fibroblasts have been identified recently as potent cytokine and chemokine producers.[3] Some of these heart-derived inflammatory mediators activate bone marrow, which produces neutrophils and monocytes. Monocytes are the main cell types infiltrating the heart during myocarditis. The knowledge from myocarditis mouse models suggests that the inflammatory monocytes (Ly6C^hi in mice) drive the damage of the heart during myocarditis, whereas the patrolling phenotype (Ly6C^lo) is protective (Figure 2).[3]

Adaptive Immune Response

The adaptive immune response is activated several days after infection and is characterized by antigen-specific T and B cells. CD8+ T cells are essential in viral clearance, whereas CD4+ T cells can play a pathogenic role in coxsackievirus B3 (CVB3)–induced myocarditis.[4] IL-17A (interleukin-17A) has been found to drive progression to cardiac fibrosis and dilated cardiomyopathy (DCM) through activation of cardiac fibroblasts and subsequent infiltration of monocytes in a murine model and in human myocarditis and DCM.[5] B cells produce virus-specific antibody, act as antigen-presenting cells activated through their Toll-like receptors, and can be a target for immunotherapy.

Autoimmune Response

Some cases of myocarditis appear to be autoimmune, as suggested by familial clustering, coexistence of autoimmune diseases in the patient, weak association with human leukocyte antigen (HLA)-DR4, presence of autoantibodies, and abnormal expression of HLA-II and adhesion molecules.[6] Subclinical myocarditis is more prevalent in patients with systemic autoimmune diseases. A chromosomal locus encoding HLA-I and HLA-II has also been identified as a susceptibility for inflammation-driven idiopathic DCM, supporting an autoimmune origin.[7] α-Myosin heavy chain IgG (immunoglobulin G) antibodies are specific to the heart and found in both patients with myocarditis and those with DCM. Antibodies reactive to mitochondria, M2 muscarinic receptor, β1-adrenoceptor,
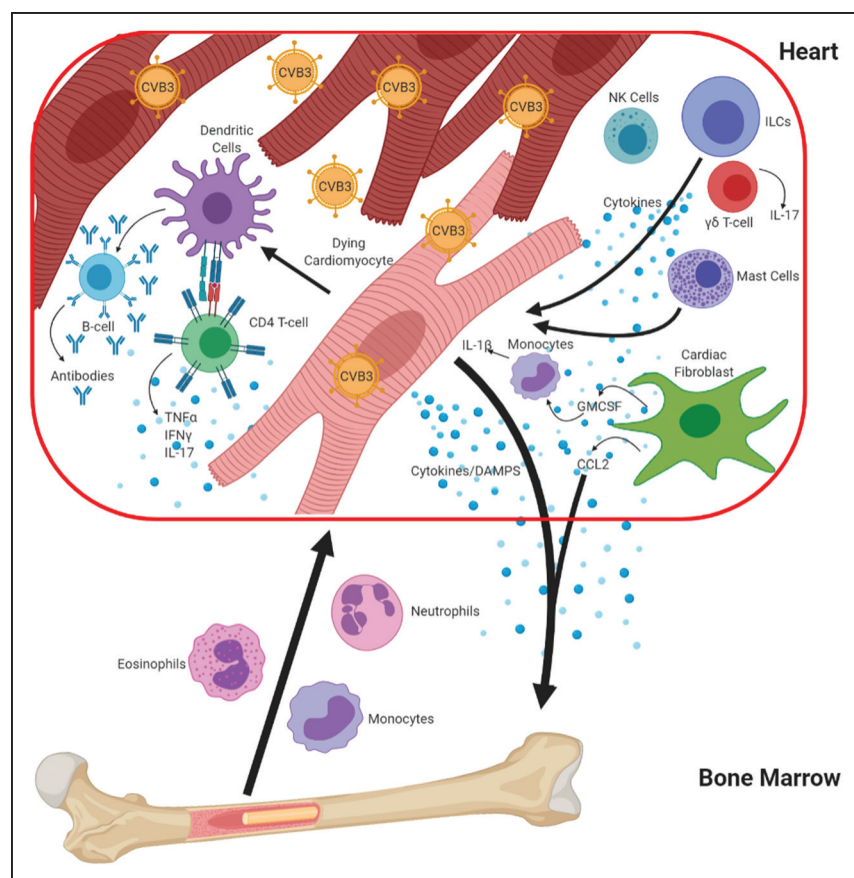
Figure 2. Immune response in the myocardium during acute viral myocarditis.
Schematic of the immune response in the myocardium during acute viral myocarditis. Coxsackievirus B3 (CVB3) infecting cardiomyocytes is followed by innate immune response, including innate lymphoid cells (ILCs), natural killer (NK) cells, gamma delta (γδ) T cells, and mast cells. IL-17A (interleukin-17A) and other inflammatory cytokines stimulate cardiac fibroblasts to secrete GMCSF (granulocyte-macrophage colony-stimulating factor) and CCL2 (C-C motif chemokine ligand 2), which then promote inflammatory monocytes trafficking to the heart. Adaptive immune response contributes to the inflammation during myocarditis. T cells produce TNFα (tumor necrosis factor-α), IFNγ (interferon-γ), and IL-17, and B cells make antibodies. DAMPS indicates damage-associated molecular patterns. Created with BioRender.com.

and troponin also have been identified by multiple groups and could affect prognosis.[6]

Cardiovascular Injury

Injury and death of cardiomyocytes and infiltration of the tissue with immune cells are the hallmarks of acute myocarditis. CVB3 protease 2A induces cardiomyocyte apoptosis and cleaves dystrophin, which contribute to the development of cardiomyopathy.[8] As inflammation subsides, the heart can recover. In some patients, the inflammation progresses to ventricular remodeling. Viral persistence may contribute to progression because the detection of enterovirus RNA portends a worse prognosis, whereas a polymorphism in the CC chemokine receptor-5 associated with enterovirus clearance reduces mortality.[9]

Murine Models of Myocarditis

Experimental murine models have contributed to the understanding of the pathogenesis of myocarditis. Two frequently used models are CVB3-induced and cardiac myosin–induced experimental autoimmune myocarditis. CVB3-induced myocarditis and experimental autoimmune myocarditis in susceptible strains progress to DCM. The main antigen identified in the CVB3 model is the cardiac myosin heavy chain. The myosin or peptides derived from myosin emulsified with Freund complete adjuvant can be used to induce experimental autoimmune myocarditis.

CAUSES

Acute myocarditis commonly has an infectious cause (Table I in the Data Supplement), with viral causes being the most prevalent. Specific viral causes have been shown by polymerase chain reaction (PCR) analysis of myocardial tissue and have demonstrated that the prevalence of specific viruses has shifted over time from predominantly adenovirus and enteroviruses to parvovirus B19 and human herpesvirus 6.[10,11] Despite this shift, a diverse array of infectious (Table I in the Data Supplement) and noninfectious (Table II in the Data Supplement) causes of myocarditis remains. More recently, during the coronavirus disease-19 (COVID) pandemic, a novel form of shock with ventricular dysfunction emerged in children and is attributed to severe acute respiratory syndrome coronavirus 2.[12,13] It is called multisystem inflammatory syndrome in children and likely involves inflammation of the heart and vasculature during or after the active infectious phase. Signs of myocardial inflammation and viral nucleic acid have been observed in autopsy cases.[14,15]

Noninfectious causes of myocarditis include autoimmunity, hypersensitivity, medications, and toxins. Autoimmune-mediated myocarditis tends to include pericarditis and systemic inflammation. In children with lupus, 10.8% can have myocarditis, pericarditis, or both combined as a part of the presenting syndrome (Table II in the Data Supplement).[16] Although very rare in children, giant cell
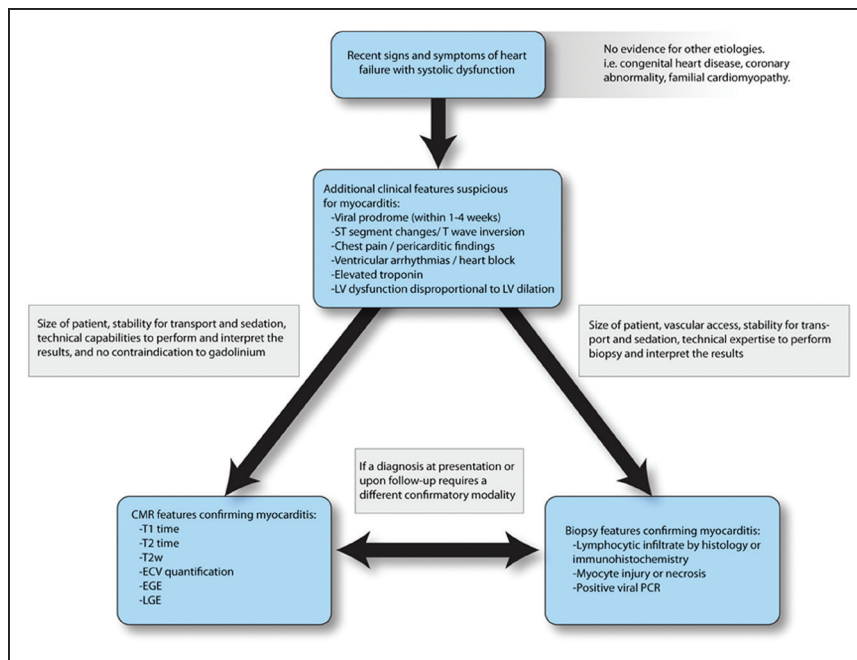
Figure 3. A simplified framework to confirm the suspicion of myocarditis. This diagnostic approach leverages various modalities, starting with clinical features followed by the application of cardiac magnetic resonance (CMR) or endomyocardial biopsy to confirm clinically suspected myocarditis. ECV indicates extracellular volume; EGE, early gadolinium enhancement; LGE, late gadolinium enhancement; LV, left ventricular; PCR, polymerase chain reaction; and T2w, T2-weighted imaging.

myocarditis is also likely autoimmune mediated and is often fulminant and fatal if not recognized.[17]

Hypersensitivity myocarditis, characterized by eosinophilic infiltrate on biopsy, has been associated most commonly with medications but can be seen with toxins, infections, and malignancies.[18] The most common medications implicated are antibiotics and agents acting on the central nervous system, although many other agents have also been identified (Table II in the Data Supplement).[18]

Immune checkpoint inhibitors are increasingly used to treat malignancies and have emerged as a cause of myocardial inflammation in adults. The exact mechanism is unclear; however, upregulation of T-cell activity is involved.[19] Although rare, drugs of abuse and toxins can cause myocardial ischemia such as from coronary vasospasm with cocaine or a direct cardiac cytopathy resulting in an inflammatory response. Given that the treatment is based on cause in noninfectious types, it is important to consider them in the differential diagnosis.

CLINICAL MANIFESTATION AND DIAGNOSIS

Myocarditis presents as several distinct clinical profiles. Typically, acute myocarditis presents with a poorly functioning ventricle with or without dilation, recent heart failure symptoms, and viral infectious symptoms in the preceding weeks.[20,21] Fulminant myocarditis presents as cardiogenic shock; tachyarrhythmias are common, and inotropic or mechanical circulatory support (MCS) may be needed.[22] Chronic persistent myocarditis occurs in the setting of cardiac symptoms such as chest pain, often with preserved systolic function, and histologic

evidence of persistent myocardial inflammation.[23] There have also been reports of pediatric patients with recurrent myocarditis, defined as episodes of acute myocarditis with intervals of clinical resolution.[24] Figure 3 provides a simplified diagnostic pathway for myocarditis. A comprehensive clinical assessment is critical because it places the presentation in a clinically suspected tier for myocarditis from which additional medical decisions on advanced diagnostics and therapy are to be made.

Signs and Symptoms

Presenting signs and symptoms (Table) have been reported in several large (n>150) pediatric series.[2,21,25] History of a preceding viral prodrome is present in about two-thirds of patients. Fever has been reported in >50% of patients at presentation in a single-center pediatric study comparing biopsy-confirmed myocarditis with DCM (58% versus 15%; P=0.002); other cardiovascular complaints were not different between groups.[26] Arrhythmias occur in up to 45% and include ventricular and atrial arrhythmias and high-grade atrioventricular block.[21,27] Syncope occurs in ≈10%.[21] Myocarditis can also present with sudden cardiac death and has been identified in 9% of young athletes with sudden cardiac death in the United States.[28]

Laboratory Testing

The use of serologic markers in cardiovascular disease is common and may assist with diagnosis, identify ongoing myocardial damage, and offer insight into prognosis.[11,29,30] However, available biomarkers lack specificity, and no biomarker can differentiate myocarditis from other causes of acute myocardial dysfunction, injury, or isch-

Table. Clinical Characteristics at Presentation With Their Reported Frequencies in Pediatric Myocarditis

History (%)	Symptoms (%)	Signs (%)
Viral prodrome (41–69)	Fatigue (25–70)	Tachypnea (52–60)
Arrhythmias (11–45)	Shortness of breath (35–69)	Tachycardia (32–57)
Syncope (4–10)	Fever (31–58)	Hepatomegaly (21–50)
Sudden cardiac death (9)	Nausea/vomiting or abdominal pain (28–48)	Respiratory distress (21–47)
	Rhinorrhea (38–44)	Murmur (26)
	Chest pain (24–42)	Gallop (20)
	Dyspnea (22–25)	Diminished pulses (16–21)
	Cough (17–44)	Edema (7)
	Palpitations (16)	Cyanosis (2)
	Diarrhea (8)	

emia.[31] Traditional markers of cardiomyocyte lysis, including creatine kinase MB and troponins, may be elevated in acute myocarditis and are readily available. Troponin I and troponin T are more commonly used in pediatrics and can be elevated (troponin leak) in children with acute myocarditis. Troponin does not appear to be a sensitive or specific enough marker of biopsy-proven myocarditis. When elevated, it is often detected at very high levels.[30] Troponin elevation has not been correlated with cardiac dysfunction or arrhythmias, but higher troponin levels have been associated with the use of extracorporeal membrane oxygenation (ECMO) and mortality.[2,27] BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-BNP) are commonly elevated at the time of presentation and are associated with cardiac dysfunction, signs of acute heart failure, and the need for cardiopulmonary resuscitation or MCS.[2] However, natriuretic peptides are generally related to heart failure, not specifically to myocarditis. Trending these biomarkers may be more useful than analyzing a single random sample other than at the time of presentation to screen for a cardiac problem. Nonspecific serum markers of inflammation, including leukocyte count, sedimentation rate, and C-reactive protein, can be elevated in cases of acute myocarditis or systemic inflammatory disorder, but normal values do not exclude an acute myocardial inflammatory process.[20]

Immunohistochemistry and viral genome analysis of the myocardium by PCR can characterize immune cells and specific pathogens (see also the Histopathology section). These tools complement basic histology and supplant the Dallas criteria, which have a high sampling error rate >25%, interreader variability in interpretation, and low prognostic value.[32,33] A positive viral culture from the myocardium has been considered the diagnostic standard in the past but is of low yield. Viral culture of peripheral specimens such as stool or urine is commonly performed but is unreliable at attributing the same agent as causative of myocarditis. Viral antibody titers are unreliable because they take time to develop during an active infection, and positivity may reflect an unrelated prior infection. Viral serology had low positive and negative predictive values in studies confirming myocarditis by biopsy, although 1 study showed a 4-fold increase in viral antibody titer correlated with infection.[32] PCR is extremely sensitive and specific and may identify the viral genome in the heart in ≈45% to 50% of suspected cases.[10,34] It can also define viral load qualitatively and has been shown to correlate with outcome in some studies. PCR can identify viral genome in peripheral blood, stool, and respiratory secretions of patients with myocarditis in about one-third of cases and is often used as a surrogate of tissue PCR to make a presumed diagnosis. However, it should be noted that the correlation of peripheral samples with disease is poor and should not be substituted for myocardial viral PCR unless it obtaining an endomyocardial biopsy is infeasible.[35] PCR is readily available for the most common viruses involved in myocarditis such as parvovirus B19, adenovirus, enteroviruses, Epstein-Barr, cytomegalovirus, and herpesvirus type-6.

Electrocardiography

Electrocardiographic features in children are variable and include sinus tachycardia, nonspecific ST-T–wave changes, T-wave inversion, ST-segment elevation, low-voltage QRS complexes in the limb leads, and atrioventricular conduction delays.[36] A pattern of myocardial injury or infarction may be seen with the ST-segment changes and may be diffuse or in a defined coronary distribution pattern. With time and myocardial damage, pathologic Q waves may be seen and were described specifically with parvovirus B19 myocarditis by PCR in 1 study.[37] Pericarditis may also be present demonstrated by ST-segment elevation and PR depression. Atrioventricular block, ventricular tachycardia and fibrillation, supraventricular tachycardias, and atrial fibrillation or flutter may occur and can be the presenting sign.[38] Myocarditis should always be ruled out in a patient with new-onset third-degree heart block.[20]

Echocardiography

Echocardiography is the first-line and most widely used imaging modality for the evaluation of cardiac structure and function in patients suspected of myocarditis. Real-time imaging and portability are key strengths for quickly assessing the severity of cardiovascular compromise, especially in children who may have limited cooperativity or hemodynamic instability. Echocardiography reliably demonstrates the variable findings associated with myocarditis, including the following[39]:

1. Subtle to profound changes in global left ventricular (LV) or right ventricular systolic function, including regional wall motion abnormalities
2. Variable degrees of LV enlargement
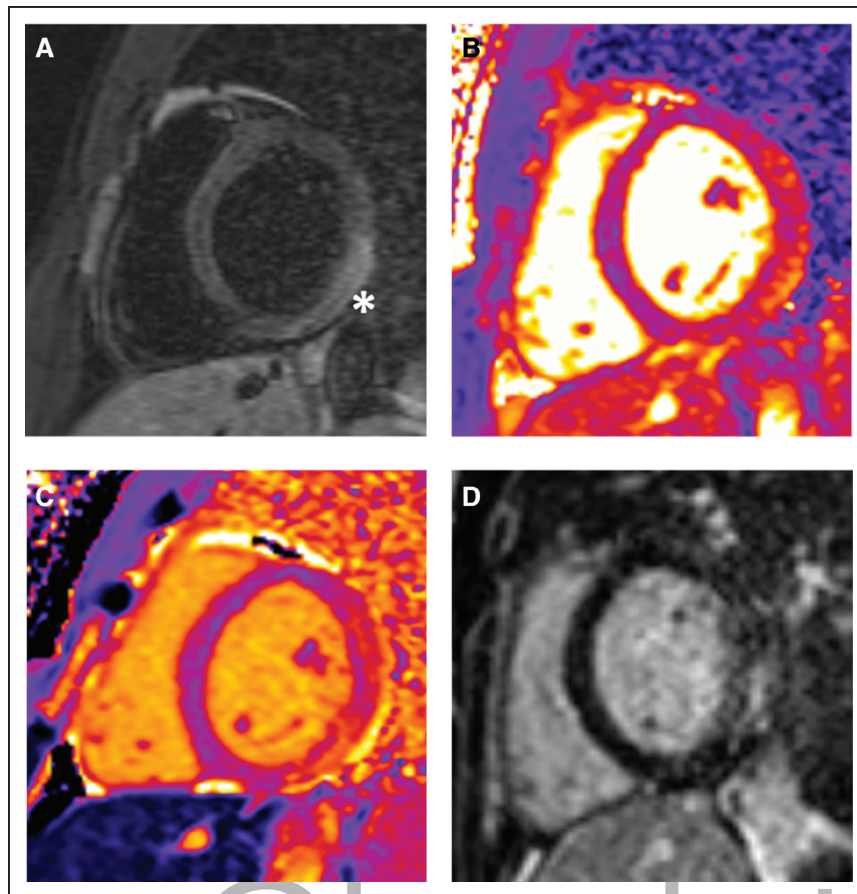3. Thickened myocardium from wall edema

Figure 4. Tissue characterization with cardiac magnetic resonance imaging in myocarditis.
T2-weighted double inversion recovery acquisition (**A**) reveals high signal intensity in the inferolateral left ventricular myocardium (*), consistent with edema. Parametric maps show elevated T2 (**B**) and T1 (**C**) times in the same region. The T1-weighted postcontrast image (**D**) demonstrates late gadolinium enhancement, suggesting myocardial necrosis or scarring.

4. Pericardial effusion
5. Intracardiac thrombus
6. Functional valvar regurgitation

Although generalized, a set of markers supportive of myocarditis would be the severity of LV systolic dysfunction and increased wall thickness that are disproportionate to the degree of LV dilation. Although it is the mainstay of diagnosis and surveillance, there are limitations to echocardiography in differentiating myocarditis from other pathogeneses. Tissue Doppler and myocardial strain can detect subtler changes in systolic or diastolic function, which may correlate with tissue pathology observed on biopsy or CMR.[40–42] LV end-diastolic dimension[43] and severity of dysfunction[2] are reported to be associated with outcomes.

CMR Imaging

Although a common indication for performing CMR in adults is to distinguish myocarditis from coronary ischemia, the main objectives in children are to identify myocardial injury and to detect inflammatory features to distinguish acute myocarditis from noninflammatory cardiomyopathies.

Given the heterogeneous and often nonspecific presentation and echocardiographic findings of myocarditis,[20] more sensitive and specific imaging techniques are

needed.[22] CMR can demonstrate markers of inflammation and necrosis that characterize myocarditis histologically. Beyond tissue characterization, CMR is the gold standard for quantification of ventricular volumes, ejection fraction, and mass.

Clinical markers of inflammation by CMR include high signal intensity on T2-weighted imaging (Figure 4A), increased T2 (Figure 4B) and T1 (Figure 4C) times denoting extracellular volume (ECV) fraction, myocardial thickening attributable to edema, and rapid uptake (early gadolinium enhancement) of contrast as a sign of hyperemia.[44] In addition to edema, T1 and ECV are markers of diffuse myocardial fibrosis in chronic disease processes such as cardiomyopathies. Measures of necrosis include contrast retention 10 to 15 minutes after injection of gadolinium, indicating either acute myocardial injury or scar formation (Figure 4D). Because of this overlap in imaging phenotype, it is important to synthesize all imaging and clinical information, including chronicity in the course, to differentiate myopathic and inflammatory changes. These imaging abnormalities may be distributed heterogeneously, necessitating sampling at multiple locations. All mapping parameters, especially ECV, are influenced by the specific CMR scanner, contrast agent and dose, and examination protocol, requiring each center to carefully evaluate whether published normative data are appli-

cable and to potentially generate their own reference values for clinical application and quality assurance.[44] Table III in the Data Supplement summarizes the CMR parameters used for tissue characterization and their differences between myocarditis and DCM or ischemic cardiomyopathy.

In 2009, the Lake Louise criteria proposed a consensus definition for the diagnosis of myocarditis in adults by CMR. The authors suggested that the diagnosis was likely if 2 of 3 criteria from T2-weighted, early gadolinium enhancement, and late gadolinium enhancement imaging were present. In 2018, these criteria were updated to include T2, T1, and ECV quantification for improved diagnostic accuracy.[45] A recent meta-analysis of adult patients yielded sensitivities of 89%, 78%, 75%, and 68% and specificities of 90%, 84%, 76%, and 96% for T1, T2, ECV, and late gadolinium enhancement, respectively.[46]

Systematic experience with CMR tissue characterization in pediatric patients with suspected myocarditis is limited by mostly small single-center studies and heterogeneity in techniques among sites in scanner hardware, contrast type, and image acquisition protocols, as well as challenges in confirming the diagnosis. In a small study of 23 patients with clinically suspected myocarditis, increased T1, T2, and ECV demonstrated sensitivities between 86% and 91% and specificities between 74% and 89%.[47] Late gadolinium enhancement was present in 86%, and 57% had signal increases on T2-weighted imaging, whereas only 13% had evidence of hyperemia, results that are consistent with a retrospective multicenter study that predated widespread parametric mapping practice.[48] Myocardial first-pass perfusion does not appear to add substantially to the diagnostic utility. The value of strain quantification by CMR feature/tissue tracking remains to be determined.[41] Persistent CMR markers of edema or fibrosis are not uncommon in pediatric patients with myocarditis; however, the prognostic implications are uncertain and remain an area of active investigation.[49]

Nuclear and Computed Tomographic Imaging

With wider availability of CMR, computed tomography and radionuclide evaluations are not routinely recommended for diagnostic evaluation of myocarditis. In situations in which there is significant overlap between features of acute coronary syndrome and myocarditis, computed tomography angiography can be used to evaluate the coronary artery anatomy. Several nuclear modalities have been used to detect myocardial inflammation in children and adults; however, accuracy is variable and in general low.[29] In both computed tomography and nuclear imaging, the exposure to ionizing radiation is an important consideration.

Histopathology

Despite advances in myocardial imaging, direct tissue examination remains the reference standard for diagnosing myocarditis. The Dallas criteria, published in 1987, provide a standard histologic framework to diagnose myocarditis, relying on the detection of inflammatory cellular infiltrates and myocyte necrosis that cannot be explained by coronary artery disease or other pathogeneses.[50] However, because of the focal nature of myocardial infiltrates and random sampling of specimens, a high false-negative rate has been reported.[33] In addition, CMR has demonstrated that myocarditis occurs predominantly in the free wall of the LV, which is inaccessible with standard endomyocardial biopsy techniques.[10] Immunohistochemistry has improved the sensitivity of detecting inflammatory cellular infiltrates. It can also demonstrate increased expression of HLA and inflammatory cellular markers to support a diagnosis of myocarditis if not apparent by basic histology.[51]

TREATMENT

Acute myocarditis in children can progress rapidly to hemodynamic compromise, sometimes even in the setting of borderline systolic function and especially with the emergence of arrhythmias.[52,53] Anticipatory care is necessary. Judicious triaging of the disposition of patients seen in ambulatory or emergency care locations for workup or for management of suspected myocarditis is crucial. It is also important to determine whether monitoring in the intensive care unit is necessary. The ability to closely monitor the cardiovascular status, including the rhythm continuously, should be considered. If the trajectory is toward hemodynamic compromise, consideration should be given to transfer to a center that provides pediatric MCS and transplantation.

A critical aspect in the early phase is monitoring for atrial or ventricular arrhythmias. Arrhythmias may be associated with a poor early outcome.[27] The management of arrhythmias is outside the scope of this statement and is covered elsewhere[54]; however, it should be noted that there are no specific antiarrhythmic medical therapies related to myocarditis. It is unclear whether treatment of myocarditis lessens the development of arrhythmias. Bradyarrhythmias and heart block are rare presentations. Temporary transvenous pacing should be considered because the rhythm disturbance may be transient but hemodynamically compromising with progression of ventricular dysfunction.[55] Cardiac monitoring in an inpatient setting is reasonable if myocarditis is suspected.

Supportive care is similar to other scenarios of acute heart failure. Low cardiac output should be treated promptly. Milrinone typically is used as first-line therapy for inotropy, whereas inotropes with vasopressor properties such as epinephrine and dopamine are generally
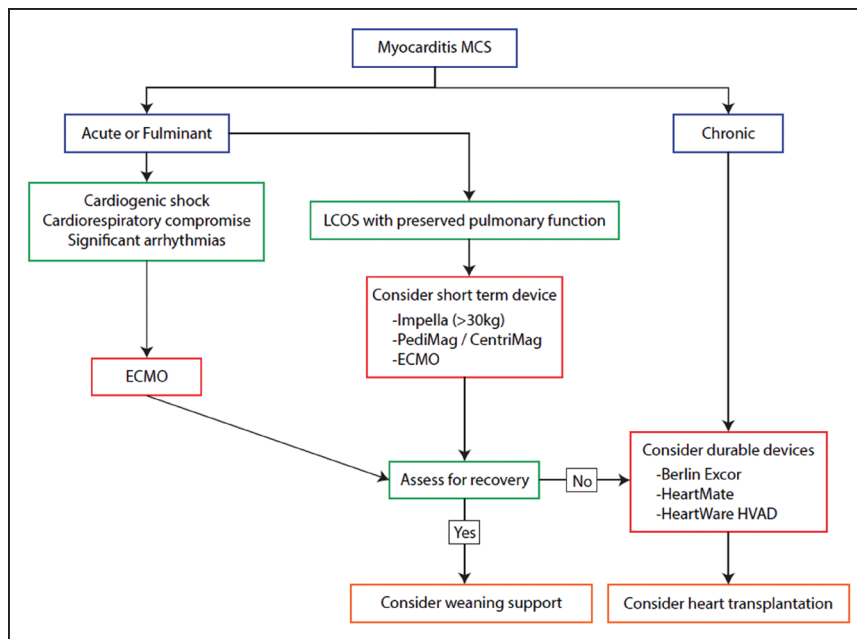
Figure 5. Potential strategy for mechanical circulatory support (MCS) in acute myocarditis.
Device names are examples of devices within the categories only and are not the only options. ECMO indicates extracorporeal membrane oxygenation; and LCOS, low cardiac output syndrome.

reserved for those with hypotension and cardiogenic shock because these agents have more chronotropic and arrhythmogenic potential.[2] Calcium chloride and vasopressin infusion can also augment perfusion pressure without adding to cardiac stimulation. Oral heart failure therapy should be initiated once the patient is beyond the acute stage of illness and shows persistent systolic dysfunction or heart failure. Because acute myocarditis leads to myocardial injury, similar to acute myocardial infarction in which reverse remodeling drugs are used even without LV systolic dysfunction, it is unclear whether the same protective approach should be taken in children with myocarditis whose LV function has normalized (see the section An Adult Perspective on Pediatric Myocarditis).

Early intervention with MCS should be considered and can be lifesaving. Thus, patients should be cared for at a pediatric center with expertise in MCS and transplantation. Registry data show that 23% of patients during the early phase of hospital admission require MCS with either ECMO or a ventricular assist device (VAD).[1] The suggested algorithm for type of MCS based on the clinical scenario is shown in Figure 5. ECMO is an attractive choice of MCS because it can be deployed emergently and because the probability of a brisk cardiac recovery in myocarditis is high compared with cardiomyopathy. Alternatively, percutaneous support with Impella has been reported with reasonable success and can be deployed expeditiously to support the LV with unloading.[56] If ECMO cannot be weaned, consideration is given to transition to durable VAD as a bridge to recovery or transplantation (Figure 5). There are no data to compare the superiority of the use of VAD preemptively (electively) or of VAD over ECMO.

Regardless of the choice of MCS, early left-sided heart decompression is important in patients with severe LV dysfunction or stunning to maximize the opportunity for recovery. A percutaneous atrial septostomy, surgical placement of a vent, or use of Impella accomplishes LV unloading. ECMO support has a 69% to 76% survival to discharge rate. Up to 24% of patients on Berlin Excor may be weaned off, and patients on VAD should be assessed serially for ventricular recovery.[20] Patients who require long-term MCS or who recover from the acute episode but develop severe chronic heart failure may require heart transplantation.[57]

Antiviral and Immunotherapy

There are insufficient data in children to permit evidence-based recommendations for myocarditis-specific immunotherapy. Nevertheless, immunotherapy is reported in numerous studies and is commonly used when practitioners are confronted with an acutely decompensated patient.[58] It remains important to recognize key features that have emerged in the study of immunotherapy to aid therapeutic decision-making even if only on an individual case basis. These features include the epidemiology of childhood myocarditis; a viral pathogenesis and acute presentation are more likely than in adults. Stages in the natural history such as active viral infection that can progress to an acute inflammatory response, persistence of viral presence detected by PCR or inflammation, and the sequela of autoimmunity may affect response to therapy. Immunotherapies such as intravenous immunoglobulin (IVIG) and corticosteroids have broad and overlapping effects. A definitive diagnosis to guide therapy can be elusive even within trials, and many studies do not report a virology workup. Last, ventricular function improves or recovers fully in many patients, making a treatment effect difficult to ascertain in uncontrolled studies.

Although IVIG is commonly used in children, it is not well studied in children or adults. IVIG is not thought to be immunosuppressive but has anti-inflammatory, anti-viral, and immunomodulatory effects and is considered safe and familiar to most pediatricians. Drucker et al[58] suggested echocardiographic and survival benefits with IVIG, but the historical control group was less acute, their LV was more remodeled, and the diagnosis of myocarditis was not well ascertained at presentation. Attempts at meta-analysis have not been informative, given small sample sizes and the quality of studies. Hospital- and scientific registry–based studies have large sample sizes but lack the details on therapy to provide outcomes related to treatment. A national registry study used propensity matching to compare IVIG and steroids separately with no treatment and showed no difference in in-hospital survival.[59] However, very few patients had CMR or biopsy to confirm a clinically suspected diagnosis. One intriguing nonrandomized controlled study treated children with clinical myocarditis in the setting of acute viral encephalitis with IVIG alone and showed dramatic improvement in echocardiography and survival.[60]

Corticosteroids are considered immunosuppressive, but they also have potent anti-inflammatory effects. Numerous studies have evaluated the impact of corticosteroids on myocarditis, including rigorously conducted randomized controlled trials in adults. These studies focused on patients with more chronicity, as more commonly seen in adults but infrequently described in the pediatric literature. The landmark study by Mason et al[61] did not show improvements in echocardiography or survival. However, Frustaci et al[62] showed improvement in LV function in 38 of 43 patients treated with prednisone and azathioprine versus 0 of 42 in the placebo group with biopsy-proven myocarditis without persistence of myocardial viral genome. These results support that immunosuppression is effective for the autoimmune phase of myocarditis without active viral infection in adults.

In children, several small studies with prednisone plus azathioprine or cyclosporine, without controls, and often without biopsy or CMR evidence of myocarditis showed improvement, typically of LV function by echocardiography. In contrast, a larger, multi-institution study using a national registry did not show a survival benefit, although echocardiographic results were not available.[59] One intriguing report described the use of anti-CD3 antibodies in the setting of acute/fulminant myocarditis (9 of 15 on MCS) along with corticosteroids and IVIG; in this study, despite the use of these potent immunosuppressive agents during the acute and presumably infectious phase, infectious complications were not observed.[63] Of the 10 transplantation-free survivors, all had significant improvement in systolic function. Without a control group, it is unclear whether the 5 who deteriorated did so as a result of propagation of viral infection in the myocardium.

Specific antiviral agents have not been rigorously tested for myocarditis. Given their known beneficial effects in noncardiac infections, it is reasonable to treat myocarditis with these agents if an active infection is diagnosed even without proof of the infection in the myocardium (Table I in the Data Supplement provides viral pathogeneses). The following are antivirals available in the United States: acyclovir for herpes simplex; ganciclovir/valganciclovir for cytomegalovirus and human herpesvirus 6; oseltamivir and baloxivir for influenza; cidofovir for adenovirus; remdesivir for severe acute respiratory syndrome coronavirus 2; and multiple options for HIV and hepatitis C. There are also reports of the antiviral efficacy of IVIG in parvovirus infections, including myocarditis, in the immunocompromised and immunocompetent host. Input from an infectious disease expert is recommended.

Although rare in children, other forms of myocarditis known to respond to immunotherapy include giant cell myocarditis, sarcoidosis, and eosinophilic myocarditis. These forms of myocarditis are known to respond to corticosteroid-based immunosuppression. Myocarditis can also be seen secondary to systemic autoimmune diseases (Table II in the Data Supplement). Therapy is typically immunosuppression and would be targeted to the underlying systemic disease in collaboration with rheumatology. Myocarditis is associated with rheumatic fever and Kawasaki disease. Their management follows that of the primary disease and is reviewed extensively in other American Heart Association statements. The emergence of COVID-19 has led to the description of a new multisystem inflammatory syndrome in children that involves the myocardium and coronary arteries in some infected patients.[12,13] Its therapy may consist of antiviral, IVIG, steroids, and other anti-inflammatory drugs used in atypical Kawasaki disease.

To summarize, patients with acute myocarditis can deteriorate rapidly. Anticipatory care includes careful triaging and admission to a ward that can monitor the cardiovascular condition closely or transfer of the patient to a center that can provide advanced pediatric cardiovascular care, including MCS and transplantation. Antiviral therapy should be considered if an active viral infection is found. Immunomodulatory or immunosuppressive therapy remains center and practitioner specific, and each center should develop its own multidisciplinary guidelines of care with ongoing review to ensure quality.

FOLLOW-UP

It is prudent to perform regular cardiology follow-up incorporating electrocardiography, echocardiography, and laboratory tests at a frequency similar to that for recently diagnosed acute heart failure from cardiomyopathy. Controversies revolve around the need for follow-up biopsy, CMR, and duration of heart failure medications. Pragmatically, if ventricular function, inflammatory biomarkers, or viral activity such as PCR from blood continues to be

abnormal, it is reasonable to perform a biopsy or CMR at follow-up. Similarly, discontinuation of reverse remodeling medications can be considered if all diagnostic testing is normal. CMR may have a role in determining the benefits of reverse remodeling medications when echocardiography is normal by demonstrating subclinical injury and fibrosis. However, the duration of normality before medication is stopped, even with normal diagnostic testing, is unclear. An injured myocardium can still remodel slowly and become myopathic later in life. In the largest follow-up of biopsy-proven and presumed myocarditis in children, Foerster et al[57] showed that 46% to 48% of patients had persistent echocardiographic systolic dysfunction, 6% to 7% died, and 17% to 19% required transplantation over a 3-year period. It is possible that in some patients with idiopathic DCM presenting in adulthood, its origin could have been undiagnosed childhood myocarditis.

Because children are active and many will recover functional capacity, exercise and activity restrictions demand special consideration. According to autopsy studies and CVB3 myocarditis murine model, myocarditis is associated with sudden cardiac death, especially with exercise.[28] The risk of sudden death may not correlate with the severity of myocardial inflammation, and sudden death has been observed even with normal systolic function after myocarditis. Patients should not participate in competitive sports while active inflammation is present.[64,65] In addition to normalization of inflammatory and myocardial injury markers, as well as ventricular function and heart failure, 24-hour Holter monitoring and exercise stress testing should be performed in athletes, but no sooner than 3 to 6 months, before they return to competition.[64–66]

ADULT PERSPECTIVE ON PEDIATRIC MYOCARDITIS

The management of acute myocarditis in adults presents many of the same challenges in the diagnosis, treatment, and screening for recurrence as in pediatric myocarditis.

Myocarditis is a disease that crosses the entire age spectrum. The incidence of myocarditis varies with age, being higher in infants and rising again in young adults.[67] The causes of myocarditis also vary by age, with older patients on multiple medications having a higher risk for hypersensitivity drug reactions. In adults, coronary atherosclerosis is an important cause of cardiomyopathy and arrhythmias that always needs to be excluded by invasive or noninvasive angiography. Recent reports of desmosomal gene variants associated with recurrent myocarditis have sparked an interest in genetic causes of myocarditis at all ages.[68]

The signs and symptoms are similar to those for children with the possible exception that a fulminant presentation seems more common in hospitalized children than adults. CMR in adults is most accurate in the first weeks after symptom onset and may not identify low-grade inflammation in chronic cardiomyopathy.[48] The risks of biopsy at experienced centers may be lower in adults (<1:1000 probability of death) than in infants and small children.

The rate of recovery from MCS in patients with cardiogenic shock is generally better than in for noninflammatory cardiomyopathies.[69] Management of systolic dysfunction consists of guideline-directed medical therapy for heart failure in all patients and various forms of immunosuppression for giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, and systemic disease–associated myocarditis. Avoidance of competitive sports based on expert opinion is the same as in children to minimize life-threatening arrhythmias, but there are few prospective studies to validate this strategy.[64] The risk of recurrent myopericarditis is 10% to 15% at 1 year in adults.[70] The TRED-HF study (Therapy Withdrawal in Recovered Dilated Cardiomyopathy–Heart Failure) reported a 44% risk of recurrent heart failure in adults discontinuing guideline-directed medical therapy with recovered, nonischemic cardiomyopathy.[71] The specific risk of recurrence of heart failure in myocarditis-related DCM is not known.

CONCLUSIONS

Myocarditis in children remains a challenging condition to diagnose and manage. Its impact on lifelong morbidity and mortality is significant. To improve its outcomes, more scientifically rigorous investigation is needed. Given the heterogeneous presentation and outcome of this condition and the various diagnostic and therapeutic options, these investigations also require a concerted, multidisciplinary effort. With improved cardiovascular diagnostic tools such as comprehensive viral PCR from tissue, biomarkers, immunohistochemistry, and CMR, formulating a set of criteria for its diagnosis based on the accuracy of testing from these studies should be top priority. Similarly, demonstrating the effectiveness of therapy requires properly designed trials in which a prerequisite is a uniform and accepted working diagnosis. We hope that this statement serves not only as an educational update but also as a unifying call to organize our efforts to better understand and treat this important pediatric condition.

ARTICLE INFORMATION

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