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Myocarditis in the pediatric population: A review

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Abstract

Myocarditis has a variable clinical presentation and there is still debate regarding accurate diagnostic criteria. Adding to the controversy surrounding this diagnosis, there is no clear consensus for the treatment or ongoing follow-up of patients with myocarditis. All of this makes the diagnosis and management of myocarditis a particular challenge in the pediatric population. Furthermore, the literature with respect to this topic is dynamic and ever-changing. In this review article, we aim to review and summarize the common clinical presentations of myocarditis, along with the latest recommendations for diagnostic criteria, treatment, and follow-up of patients with myocarditis.

KEYWORDS
guidelines, myocarditis, pediatrics

1 | INTRODUCTION

Myocarditis has been defined as an "inflammatory disease of the heart muscle which is diagnosed by established histological, immunologic, and immune-histological criteria."[1] It has a variable clinical presentation and there is still debate regarding accurate diagnostic criteria.[2-4] The true incidence of myocarditis is difficult to ascertain because of its frequent sub-clinical presentation, though autopsy studies have reported the incidence to be approximately 0.12%-12%.[5,6] Most studies of acute myocarditis report male predominance, primarily young adults.[7,8] In the pediatric population, it is more common and has a poorer prognosis in children less than two years of age as compared to older children.

Myocarditis is commonly associated with abnormalities in electrocardiograms (ECG), noninvasive cardiac imaging, and cardiac biomarkers. However, these abnormalities may not always be present in a patient diagnosed with myocarditis. Adding to the controversy surrounding this diagnosis, there is no clear consensus for the treatment or ongoing follow-up of patients with myocarditis. All of this makes the diagnosis and management of myocarditis a particular challenge in the pediatric population. In this review, we aim to review and summarize the latest recommendations for diagnostic criteria, treatment, and follow-up of patients with myocarditis.

2 | DIAGNOSIS

2.1 | History and physical examination

Though it is common to have physical examination abnormalities in a patient with myocarditis, the absence of examination findings does not preclude its diagnosis. The most common presenting symptom described is tachypnea.[9] It is also common to have gastrointestinal symptoms such as abdominal pain and vomiting. Such vague and nonspecific gastrointestinal symptoms may make the path to diagnosis more difficult.[10,11] The presentation of myocarditis may often mimic the presentation and findings of acute coronary syndrome. Patients usually present with chest pain and dyspnea with ECG changes and elevated cardiac enzymes may be suggestive of myocardial ischemia.[12] Echocardiography often reveals either normal function or mild reduction in the ejection fraction with normal left ventricular size.[13] Unfortunately, the first presentation of myocarditis may also be sudden death. Reports in the United States have documented myocarditis as a cause of sudden death in as many as

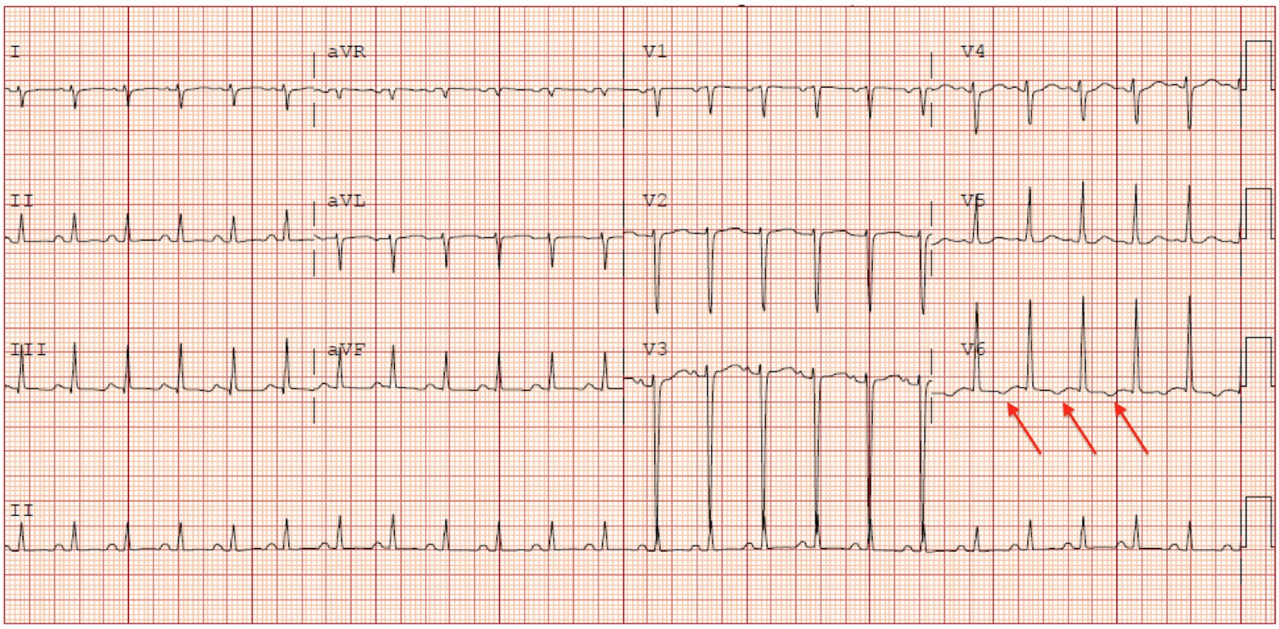

FIGURE 1 T wave inversion in the lateral leads of a 12-year-old female presenting with myocarditis. T wave inversion in lateral leads is a sign of left ventricular strain which may be indicative of myocarditis

9% of athletes in whom a cardiovascular event was documented.[14] One autopsy study found myocarditis to be the cause of 9% of infant deaths which were previously labeled as sudden infant death syndrome.[15]

A high index of suspicion should be maintained for giant cell myocarditis in patients with acute myocarditis who is present with severe heart failure, arrhythmias, and do not respond to therapy within 1-2 weeks. This may be confirmed by an endomyocardial biopsy (EMB) and has a poor prognosis if early treatment is not initiated. Therefore, early detection is essential as it may be responsive to immunosuppression.[16]

2.2 | Electrocardiography

An abnormal ECG has a high positive predictive value for the diagnosis of myocarditis but not a high negative predictive value.[10] The ECG abnormalities are variable and include nonspecific ST-T wave changes, ST-segment elevation, low voltage complexes in the limb leads, and atrioventricular conduction delays (Figure 1). Arrhythmias associated with myocarditis may range from premature contractions to complete atrioventricular block.[17] Myocarditis should always be ruled out in a patient with new-onset third-degree heart block.[18] Studies have highlighted variable rates of recovery of atrioventricular conduction. In one study, the recovery of atrioventricular (AV) block conduction occurred in 67% of children with myocarditis, with an average time to recovery being 3.3 ± 2.8 days, however 27% required permanent pacemakers, as indicated by the persistent AV block lasting longer than 1 week.[17] A large study (nine-year single-center experience) demonstrated that 22% of patients with high-degree AV block following myocarditis did not recover AV conduction.[19]

2.3 | Biomarkers

Nonspecific inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are often elevated in myocarditis, but these markers have a low negative predictive value.[20] Elevated troponin T and I may be observed in children with myocarditis.[21,22] One pediatric study found that serum aspartate aminotransferase was commonly elevated in patients with myocarditis.[9] B-type natriuretic peptide may be elevated in myocarditis and is believed to be secondary to ventricular enlargement and stretch of the cardiac myocytes. While in nonspecific, its elevation may aid in establishing a cardiac cause in children.[23,24] The monitoring of trends of these biomarkers is more important than obtaining a single spot value.

2.4 | Echocardiography

Echocardiography is the most common noninvasive tool to evaluate the ventricular function in the pediatric population. A dilated cardiomyopathy phenotype with left ventricular dilatation and diminished ejection fraction is the most common echocardiographic finding associated with myocarditis.[25] It is not uncommon to detect segmental wall motion abnormalities or global dysfunction.[26] Studies in the United States and Australia have shown that myocarditis may account for 27%-46% of newly diagnosed cases of dilated cardiomyopathy.[27,28] The presence of pericardial effusion may indicate accompanying pericardial involvement and maybe a clue to the diagnosis. Though more attention is paid to the left ventricle in a patient suspected of having myocarditis, the assessment of right ventricular function is equally important as it has been described as a predictor of the outcome. Studies have demonstrated that the likelihood of

TABLE 1 Typical echocardiographic features of classic vs fulminant myocarditis

Classic myocarditis	Fulminant myocarditis
• Left ventricular dilation • Reduced ejection fraction • Segmental wall motion abnormalities or global dysfunction may be observed • Pericardial effusion may indicate concomitant pericarditis	• Normal left ventricular cavity size • Reduced left ventricular ejection fraction • Increased septal thickening

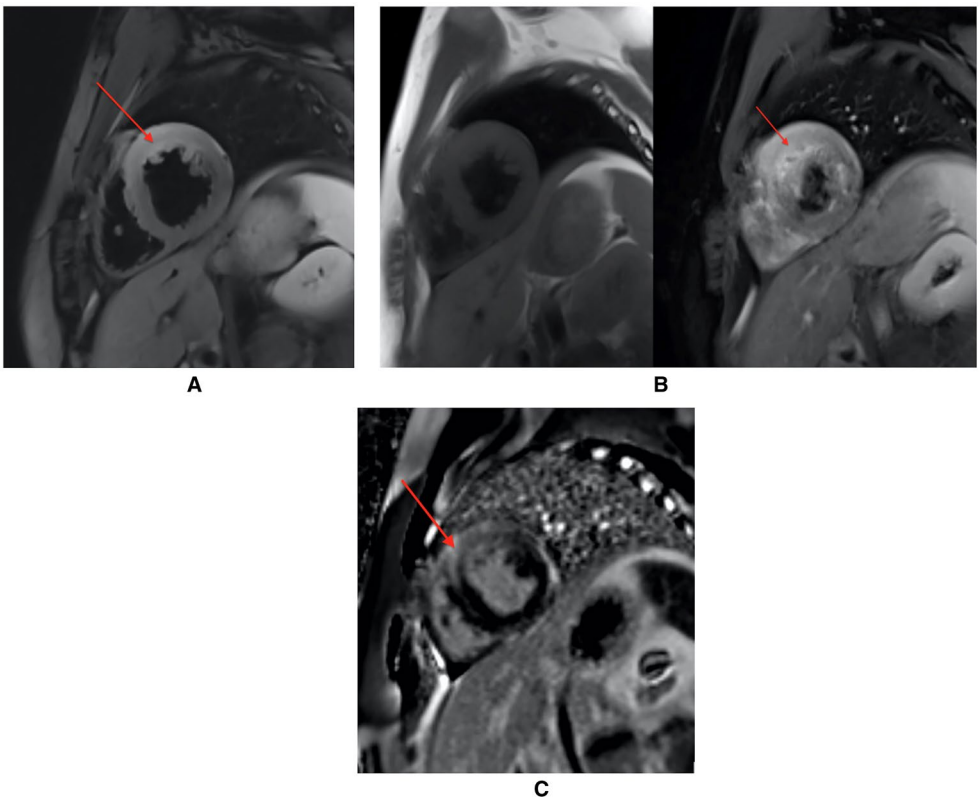

FIGURE 2 **(A)** T2 weighted cMRI demonstrating edema (red arrow) in a 15-year-old male with myocarditis. **(B)** T1 weighted cMRI (precontrast and postcontrast) demonstrating hyperemia (red arrow) in a 15-year old male with myocarditis. **(C).** Late gadolinium enhancement demonstrating fibrosis (red arrow) in a 15-year-old male with myocarditis

death or cardiac transplantation was greater in patients with abnormal right ventricular function.[29]

Fulminant myocarditis is a distinct symptom complex, and when supportive care is administered in a timely fashion, typically enjoys a higher rate of complete recovery of function. It may present with a history of recent viral illness followed by sudden-onset heart failure usually within 2-4 weeks and usually has more severe ventricular dysfunction.[30,31] In contrast to classic myocarditis, it has an echocardiographic phenotype of reduced left ventricular ejection, normal left ventricular cavity size, and increased septal thickening.[32] The relatively better long-term prognosis of fulminant myocarditis has been described in studies (Table 1).[33]

Often, there is a lack of distinguishing features between acute myocarditis and dilated cardiomyopathy with the diagnosis of myocarditis often being missed in cases of preserved left ventricular function. A study demonstrated that speckle tracking imaging may be an important echocardiographic tool for a comprehensive assessment of left ventricular myocardium.[34] This study demonstrated decreased longitudinal strain in patients with biopsy-proven myocardial inflammation even in the presence of preserved left ventricular systolic function. Other studies have also demonstrated the utility of strain echocardiography in these situations.[35]

2.5 | Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (cMRI) is currently considered to be the noninvasive gold standard for diagnosing myocarditis and is only secondary to an EMB. cMRI can detect tissue injury, including edema, hyperemia, and fibrosis[36] (Figure 2A–C). T2-weighted imaging is used for the determination of myocardial edema,[37] while T1 sequences obtained soon after the gadolinium injection (early enhancement) are used for the assessment of hyperemia.[36] The late gadolinium enhancement suggests the presence of myocardial fibrosis.[38]

T2-weighted imaging can detect tissue edema using water-bound protons as the contrast mechanism. This results in a high signal intensity of affected tissue. The edema in patients with myocarditis is often global, thus emphasizing the importance of analyzing the entire myocardium.[39] New developments, including a triple inversion press hold sequence with short acquisition time (STIR), have led to better imaging quality. Abdel-Aty et al demonstrated that an increase in T2 signal intensity by STIR imaging was able to accurately distinguish patients with suspected myocarditis from control subjects.[37]

Another important feature of tissue inflammation is local vasodilation leading to an increased uptake of contrast during the early phase. Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) is a T1-enhancing contrast agent which enhances membrane permeability resulting in an increase in the volume of distribution. Because these agents distribute rapidly into the interstitial space, this phase lasts for a brief period after the contrast administration. Contrast-enhanced T1-weighted MRI during this time is used to assess myocardial hyperemia.[40]

Irreversible myocardial injury is characterized by late gadolinium enhancement (LGE). In the initial stages of necrosis, gadolinium enters the cells through the injured cell membranes.[41] This increases its volume of distribution and helps to visualize areas of tissue necrosis. After the inflammatory clearance of necrotic regions, viable tissue is replaced by fibrocytes. This distribution of gadolinium enables the visualization of the late sequelae of inflammatory tissue damage.

The diagnosis of myocarditis by cMRI is made by The Lake Louise criteria which were recently revised (Table 2).[36,42] The revised criteria state that the diagnostic accuracy of myocarditis can be significantly improved by combining a positive T2 cMRI finding (edema) with at least one additional T1-based tissue characterization technique (hyperemia or LGE).

A recent meta-analysis pooled the results of seven diagnostic studies using EMB as the standard with the aim of comparing it with the Lake Louise Criteria of cMRI.[43] The meta-analysis showed only moderate diagnostic efficacies of the Lake Louise Criteria and its individual components for diagnosing myocarditis. Specifically, the AUCs for global relative enhancement, edema ratio, late gadolinium enhancement, and Lake Louise Criteria were 0.71, 0.72, 0.67, and 0.70, respectively. The subgroup analysis suggested that the sensitivities, specificities, and diagnostic accuracies of the Lake Louise Criteria were similar in patients with both acute and chronic myocarditis. These results highlight the need for the development of novel cMRI-related parameters and novel imaging techniques for the diagnosis of myocarditis.

2.6 | Endomyocardial biopsy

The first pathological definition of myocarditis was the Dallas criteria[44] (Table 3). However, these criteria are limited by a high interobserver variability, need for multiple samples from preferably different locations, and perhaps sample error in which a tissue sample location may not adequately capture a disease process that is not homogenous.[45] Recently, immunohistochemistry techniques have improved the detection of inflammation in endomyocardial biopsies. Inflammation in an EMB specimen is defined by the detection of mononuclear infiltrates with >14 cells/mm^2, with enhanced expression of HLA class II molecules[1] (Figure 3).

The current recommendations state that an EMB should only be performed in patients with new-onset heart failure <2 weeks with hemodynamic compromise irrespective of left ventricular dilatation; heart failure of 2 weeks to 3 months duration with a dilated left ventricle, ventricular arrhythmias, and high-grade AV block; or symptoms unresponsive to treatment within 1-2 weeks.[16] The final two scenarios are commonly seen in giant cell myocarditis which has a poor prognosis but is usually responsive to the immunosuppressive treatment.[46] While an EMB is the gold standard for diagnosing myocarditis, it is important to be cognizant of the risks associated with it including the risks of sedation and anesthesia, especially in

TABLE 2 Diagnosis of myocarditis by cMRI (original and revised Lake Louise Criteria)[36]

Original Lake Louise Criteria
In the setting of clinically suspected myocarditis, cMRI findings are consistent with myocarditis if two of the following are present: 1. Regional or global myocardial signal intensity increase in T2 weighted images 2. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1 weighted images 3. Areas with high signal intensity in a nonischemic distribution pattern in late gadolinium enhancement images
Revised Lake Louis Criteria
cMRI findings are consistent with myocarditis if the following criteria are met: 1. Regional or global myocardial signal intensity increase in T2 weighted images or increase in the myocardial T2 relaxation time AND one of the following two criteria: 2. The regional or global increase of the native myocardial T1 relaxation time 3. Areas with high signal intensity in a nonischemic distribution pattern in late gadolinium enhancement images

TABLE 3 Classification of myocarditis by endomyocardial biopsy using the Dallas criteria[43]

First biopsy	1. Myocarditis with/without fibrosis 2. Borderline myocarditis (re-biopsy may be indicated) 3. No myocarditis
Subsequent biopsies	1. Ongoing (persistent) myocarditis with or without fibrosis 2. Resolving (healing) myocarditis with or without myocarditis 3. Resolved (healed) myocarditis with or without myocarditis

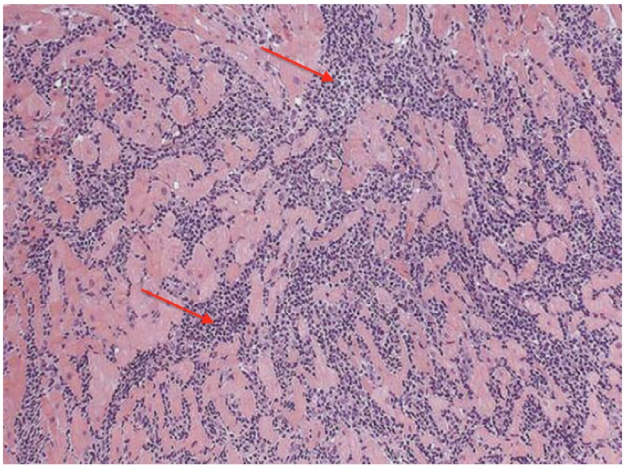

FIGURE 3 An endomyocardial biopsy specimen of a 15-year-old male with myocarditis. This biopsy specimen demonstrates diffuse neutrophilic infiltration (red arrows) indicative of myocardial inflammation

TABLE 4 Three-tier classification scheme for the diagnosis of myocarditis[48]

Classification	Criteria
Possible subclinical acute myocarditis	In the clinical context of possible of myocardial injury without cardiovascular symptoms but with at least one of the following: 1. Biomarkers of cardiac injury raised 2. ECG findings suggestive of cardiac injury 3. Abnormal cardiac function on echocardiogram or cardiac MRI
Probable acute myocarditis	In the clinical context of possible of myocardial injury with cardiovascular symptoms and at least one of the following: 1. Biomarkers of cardiac injury raised 2. ECG findings suggestive of cardiac injury 3. Abnormal cardiac function on echocardiogram or cardiac MRI
Definite myocarditis	Histological or immune-histological evidence of myocarditis

a patient with significantly diminished systolic ventricular function. Other risks associated with EMB include catheter induced injury, prolonged bleeding, arrhythmias and conduction abnormalities, damage to the tricuspid valve, and in the extreme case perforation of the ventricle.[47] Recently, Sagar et al developed a 3-tier classification for the diagnosis of myocarditis based on the histological or immune-histological evidence of myocarditis, symptoms, and echocardiogram/cMRI/biomarker/ECG findings (Table 4).[48]

3 | TREATMENT

3.1 | Medical management (Table 5)

Supportive therapy is the mainstay of therapy in myocarditis with treatment of heart failure based on published guidelines.[4,49,50] This includes the use of diuretics for preload reduction, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for afterload reduction and β-blockers. Human studies, especially in pediatrics, on the use of a conventional heart failure regimen is lacking. However, multiple animal models have demonstrated the potential benefit with the use of ACE/ARB[51] and β-blockers, especially carvedilol.[52] ACE inhibitors should be used for asymptomatic left ventricular dysfunction and a combination of ACE inhibitors and β-blockers with aldosterone antagonists in symptomatic heart failure.[50,53] Carvedilol was shown to protect against acute experimental autoimmune myocarditis in rats. This cardioprotective effect of carvedilol was believed to be secondary to its antioxidant properties and resultant suppression of inflammatory cytokines. Diuretics reduce preload and hence act as anticongestive medications particularly in the setting of a dilated cardiomyopathy phenotype. One study demonstrated that torsemide (a loop diuretic) actually reduced the progression of myocarditis to dilated cardiomyopathy in rats by altering the progression of cardiac remodeling.[54] In a follow-up study, the authors demonstrated that the treatment with torsemide significantly improved the survival rate and LV function in rats with experimental autoimmune myocarditis when compared to furosemide.[55] Aldactone is an aldosterone antagonist which has also shown to be beneficial in the long-term treatment of patients with heart failure.[56] In a mouse model, eplerenone (an aldosterone antagonist) was also shown to have anti-inflammatory effects and suppressed genes related to mast cells and cardiac remodeling.[56]

Digoxin is not recommended for the treatment of acute myocarditis because studies in mice have shown increased myocardial injury.[57] In mice treated with digoxin, IL-1 beta and TNF-alpha levels were significantly higher than in the control group, suggesting that digoxin may worsen the inflammation associated with viral myocarditis.[57] The use of nonsteroidal anti-inflammatory drugs is also controversial in this patient population. A mouse model study showed that the indomethacin decreased interferon production, increased coxsackievirus four titers, and enhanced the virulence of coxsackievirus B4.[58] Another similar mouse study demonstrated increased mortality of infected mice (coxsackievirus B3) treated with ibuprofen as compared to uninfected mice and infected/untreated mice.[59] However, nonsteroidal anti-inflammatory drugs may be used discriminately in patients with coexisting signs of pericarditis and/or pericardial effusion.[60] The clear benefit of nonsteroidal anti-inflammatory drugs in the treatment of pericarditis is difficult to extrapolate to acute myocarditis and it may be reasonable to use these agents cautiously when the clinical picture is one of the myopericarditis.[60]

Myocarditis is also a common cause of ventricular arrhythmias which are often difficult to control. This can occur both in its acute and chronic phase. In the acute phase, treatment is usually largely supportive.[61] In patients with chronic myocarditis, therapy is usually limited to the treatment of arrhythmias and implantable cardioverter-defibrillator (ICD) for higher risk cases.[62] For patients with complete or high-grade atrioventricular block which does not

TABLE 5 Medical management for myocarditis

Medication	Indication
Diuretics	Anticongestive therapy for relief of symptoms
Angiotensin-converting enzyme inhibitors	Asymptomatic left ventricular dysfunction
B-blockers	Added when there is symptomatic heart failure
	May be considered for ventricular ectopy
Aldosterone antagonists	Added when there is symptomatic heart failure, beneficial in the long term
	May be considered for asymptomatic left ventricular dysfunction
IVIG	No recommendation for the routine use in myocarditis
Immunosuppressive therapy	No recommendation for the routine use in myocarditis, useful for the management of giant cell myocarditis

recover, pacemaker implantation decisions should be based on published guidelines for device-based therapy.[62]

Some patients may require positive pressure ventilation to reduce cardiac demand and left ventricular afterload.[63] Those with more severe cases of myocarditis may require extracorporeal membrane oxygenation (ECMO) or ventricular assist devices. ECMO may also be used as a bridge to transplant in cases that progress to dilated cardiomyopathy.[64] A permanent pacemaker is indicated if the complete heart block does not resolve within 1 week.[46] Ventricular arrhythmias are treated based on current guidelines, with β-blockers being the most common therapy.[61]

3.2 | Immune suppression and immune modulation

Immune therapy remains as an area of great controversy in the treatment of pediatric myocarditis. Intravenous immunoglobulin (IVIG) has antiviral, anti-inflammatory, and immunomodulatory effects.[18] A pediatric study looking at the use of IVIG for myocarditis showed that the use of high-dose IVIG is associated with improved recovery of left ventricular function and enhanced survival for the first year post presentation.[65] However, the study had several limitations including the difficulty in the discrimination of acute myocarditis from the acute presentation of cardiomyopathy. Furthermore, the data for the hospital course and outcomes were collected retrospectively and all patients were not studied in the same time period leading to the probability of selection bias. In the only other pediatric trial to date, 26 children (admitted on Monday-Friday) with acute encephalitis and myocarditis were given IVIG for five consecutive days, and the controls admitted on other days of the week received no therapy.[66] The incidence of event-free survival at follow-up was 96% in the treated group and 77% in the control group. Follow-up continued until hospital discharge and LVEF at discharge was significantly higher in the treated group vs the control group (49.5% vs 35.9%; *P* value = .001). However, this trial had a high risk of bias and only included patients with both myocarditis and encephalitis––a condition commonly caused by enterovirus 71 infection. Though evidence from this pediatric study demonstrated a possible benefit of IVIG, this was limited to a very selective subset of patients. Further randomized controlled studies are required prior to recommend the routine use of IVIG for presumed viral myocarditis in the pediatric population.

A randomized prospective placebo-controlled trial (the intervention in myocarditis and acute cardiomyopathy study) in the adult population evaluated whether IVIG improved left ventricular ejection fraction (LVEF) in patients with recent onset idiopathic dilated cardiomyopathy or myocarditis.[67] EMB detected myocarditis in 16% of patients and there was no significant difference in LVEF for 6 or 12 months. Both control and study groups demonstrated an increase in LVEF (>10%) during the study period. This study showed that in adults with recent-onset dilated cardiomyopathy, IVIG does not lead to an improvement in LVEF. Gullestad et al also studied the efficacy of IVIG in a randomized controlled trial of adult patients with chronic dilated cardiomyopathy.[68] IVIG therapy was associated with significant improvement in LVEF for 6 months in the study but not in the control group. These studies reflect the wide variations in the subset of patients studied to determine the efficacy of IVIG for viral myocarditis along with their variable results. Based on the studies conducted so far, no recommendations can be made for the routine use of IVIG for viral myocarditis though it continues to be used commonly.

The first immunosuppressive trial of patients with unexplained dilated cardiomyopathy was performed by Parrillo et al. Reactive patients (based on histopathology) were treated with prednisone 60 mg daily for 3 months, and the majority of these patients had an improvement in LVEF.[69] This improvement was not sustained for 6 and 9 months as the control group similarly increased in LVEF. A randomized, placebo-controlled trial (The Myocarditis Treatment Trial) was performed in adults with histologically proven myocarditis in whom immunosuppressive (prednisone with cyclosporine or azathioprine) treatment resulted in no change in LVEF for 6 months and no long-term difference in transplantation-free survival.[70] In addition, the improvement in LVEF was similar in both the treatment and control groups. They concluded that based on the results they could not recommend the routine treatment of myocarditis with immunosuppressive drugs. Immunosuppressive therapy, however, remains as an important management strategy for giant cell myocarditis.[71]

In spite of this, the immunosuppressive therapy continues to be used frequently (the use of prednisone in approximately 25% of the cases) in the United States.[72] Recent immunohistochemical studies have led to an increased focus on inflammatory cardiomyopathy rather than biopsy-proven myocarditis. Wojnicz et al randomized patients with dilated cardiomyopathy with increased HLA antigen expression on biopsy to prednisone/azathioprine or placebo and noted

the improvement in LVEF after 3 months of treatment.[73] Frustaci et al treated patients (histological evidence of myocarditis and symptoms >6 months) with prednisone/azathioprine and found that a significant number of patients had an improvement in LVEF after 6 months.[74] Interestingly, 85% of the nonresponders had evidence of some virus in the myocardium leading them to suggest that patients with evidence of inflammation, chronic symptoms, and the absence of virus may be the ideal group to target with immunosuppression. A subsequent randomized, placebo-controlled trial in patients with dilated cardiomyopathy demonstrated that the majority of patients improved after six months of treatment.[75]

There has been recent interest in interferon-α and interferon-β as possible therapeutic options for myocarditis. Interferon-α was demonstrated to lead to a significant increase in LVEF in the treatment group in a single-center, randomized trial as compared to placebo or thymomodulin.[76] However, there was no difference in mortality between the two groups. Interferon-β has been shown to have benefit in patients with PCR-detected viral genome on EMB.[77] However, the efficacy of these agents need to be confirmed in larger studies.

3.3 | Therapy for advanced heart failure

Myocarditis may progress to severe heart failure unresponsive to conventional medical therapy. The initial therapy in these cases is the initiation of inotropic support. However, even intense medical therapy may also fail and these patients often require mechanical circulatory support, the most common of which is ECMO. Though ECMO can provide effective short-term (<2 weeks) support, survival is poor in patients requiring >2 weeks of support in the ELSO registry.

Ventricular assist devices (VADs) are being increasingly used in pediatric myocarditis with a favorable initial experience.[72,78] Currently, the pulsatile Berlin Heart EXCOR is the most commonly used VAD in the pediatric population, and it allows support for infants as small as 3.5 kg. The primary use of pediatric VADs is as a bridge to heart transplantation. In the Berlin EXCOR trial, patients on the device had approximately 8% mortality rate with the most common adverse events being a major bleeding, infection, and thromboembolic stroke.[79]

4 | FOLLOW-UP AND RESTRICTIONS

Guidelines for follow-up and sports restriction were initially based on the Bethesda conference 2005 recommendations for activity restriction in athletes with cardiovascular disease.[80] The most recent recommendations are based on the "AHA/ACC Scientific Statement for Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities" from 2015.[81] The guidelines state that athletes with an acute clinical syndrome consistent myocarditis should be withdrawn from all competitive sports for 3-6 months following the onset of clinical symptoms. The guidelines further state that athletes may return to competition after this period of time if: (a) the left ventricular systolic function has returned to normal; (b) serum markers of myocardial injury, inflammation, and heart failure have normalized; and (c) clinically relevant arrhythmias such as frequent or complex repetitive forms of ventricular or supraventricular ectopy are absent in Holter monitoring and graded exercise ECG's. It is controversial whether the resolution of myocarditis-related LGE by cMRI is required prior to return to competitive sports.

The data on long-term follow-up of myocarditis are limited in the pediatric population. A study looking at long-term survival following immunosuppressive therapy (cyclosporine and prednisone) as compared to conventional therapy showed that there was 83% survival at 13-year follow-up in patients receiving immunosuppressive therapy shortly after diagnosis.[82] This is in contrast to the randomized study in the adult population where there was a 44% survival at a five-year follow-up.[7] However, the study in the pediatric population had limitations of lack of a matched control group and the fact that myocarditis patients already had high survival rates. A recent study evaluated 1542 pediatric patients who were hospitalized for acute myocarditis.[83] They were divided into three groups: Those receiving neither steroid nor IVIG; those receiving high-dose steroid alone; and those receiving IVIG alone. There were no significant differences in baseline characteristics between the groups (age, heart failure medications, and inotropic agent use). There was no significant difference in in-hospital complications or in-hospital mortality rates between patients who received high-dose steroids as compared to those who did not. Furthermore, no significant differences could be elucidated in the incidence of heart failure hospitalization, cardiovascular death, and all-cause mortality in between the groups. When comparing patients who received IVIG alone as compared to those who did not, there was no significant difference in the rates of heart failure hospitalization or in-hospital mortality. This well-matched retrospective cohort study revealed that both immunotherapies (high-dose steroids and IVIG) might not affect the real-world rates of in-hospital mortality and postdischarge hospitalization for late heart failure. In addition, studies have attempted to define predictors of mortality after acute myocarditis. Such a study in adults demonstrated that LGE by cMRI is the best independent predictor of death in patients with biopsy-proven viral myocarditis. Other factors such as symptoms or type of virus isolated from EMB were not predictors of mortality.[84] Moreover, a study in the pediatric population demonstrated that children with myocarditis having hypotension, elevated Troponin I, brain natriuretic peptide, and decreased ejection fraction have higher mortality and the findings of NYHA class IV dyspnea, higher levels of brain natriuretic peptide and decreased ejection fraction are independently related to worse outcomes.[85] This is similar to a study in the adult population which suggested that a creatinine clearance <60 mL/min, an age ≥50 years, ventricular tachycardia, an NYHA classification ≥3, male gender, and a Troponin T ≥50 μg/L were independent risk factors for in-hospital mortality.[86] These variable findings

underscore the difficulty in assessing the long-term outcomes of pediatric myocarditis after various therapies. Further studies with a robust, prolonged follow-up is required to accurately characterize patient characteristics and treatment modalities which may affect long-term outcomes.

5 | CONCLUSION

Myocarditis remains as a common diagnosis in the pediatric population with significant variation in clinical presentation. Remarkable strides have been made in noninvasive imaging to assist with its diagnosis; however, further refinements are essential to consistently and accurately diagnose myocarditis. The treatment of this potentially life-threatening disease is not standardized and studies in the pediatric population are either lacking or have inherent limitations. Further randomized clinical trials are essential to determine the subset of patients who would benefit from immunoglobulin therapy, immunosuppression, or both. With the increasing use of advanced mechanical support, the hope is that the mortality rates of the sickest patients requiring such support will continue to decline.

CONFLICT OF INTEREST

The authors declare that they have no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Soham Dasgupta, Glen Iannucci, Chad Mao, Martha Clabby, and Matthew Oster contributed equally to the genesis of the research design, analysis and interpretation of data, initial drafting of the manuscript and review, and approval of the submitted and final version.

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