Treatment and prognosis of myocarditis in children

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Literature review current through: **Dec 2023.**
This topic last updated: **Jun 28, 2023.**

INTRODUCTION

Myocarditis is an inflammatory disease of the myocardium. Myocardial inflammation results in ventricular dysfunction, which can cause heart failure symptoms, hemodynamic compromise, and life-threatening arrhythmias.

Children with myocarditis are at risk for considerable morbidity and mortality.

The natural course, management, and prognosis of myocarditis in children are reviewed here.

The causes, incidence, clinical manifestations, and diagnosis of myocarditis in children are discussed separately.

Table 433-3 -- COMMON CAUSES OF MYOCARDITIS

INFECTIOUS		IMMUNE-MEDIATED		TOXIC
Viral	Adenovirus Parvovirus Coxsackievirus Hepatitis C virus Human immunodeficiency virus	Autoantigens	Churg-Strauss syndrome Inflammatory bowel disease Giant cell myocarditis Diabetes mellitus Sarcoidosis Systemic lupus erythematosus Thyrotoxicosis Takayasu arteritis	Anthracyclines Cocaine Interleukin-2 Ethanol Heavy metals
Bacterial	*Mycobacteria* *Streptococcus* spp. *Mycoplasma pneumoniae* *Treponema pallidum*			
Fungal	*Aspergillus* *Candida* *Coccidioides* *Cryptococcus* *Histoplasma*	Hypersensitivity	Wegener granulomatosis Sulfonamides Cephalosporins Diuretics Tricyclic antidepressants Dobutamine	
Protozoal	*Trypanosoma cruzi*			
Parasitic	Schistosomiasis Larva migrans			

Data from Feldman AM, McNamara D: Myocarditis, N Engl J Med 343:1388–1398, 2000; Magnani JW, Dec GW: M treatment, Circulation 113:876–990, 2006.

➢ **Virus act on myocardium in three phases.**

1) **Virus Replication Or Acute Phase**

2) **Autoimmune Injury Phase**

3) **Dilated Cardiomyopathy Phase Or Chronic Phase**

Pathogenesis

Viral infection phase

Is often reported as a prodromal presentation of fever, myalgia , and malaise several days prior to the onset of symptoms of heart dysfunction.
Respiratory and gastrointestinal symptoms are also common in this phase.
Viral infection may result in direct myocyte injury .

The use of antiviral agents has been proposed; however, their efficacy is unproven in the treatment of myocarditis.

Autoimmunity and inflammatory phase

Is caused by activation of the host immune system by the primary viral infection.
Myocyte injury results from inflammation triggered by T cell and cytokine activation, which can be detected by endomyocardial biopsy.

Myocyte injury leads to impaired ventricular function, heart failure, and/or arrhythmias.

In most patients, the acute immune response declines with viral elimination and left ventricular function recovers without sequelae within the first two to four weeks .

During this phase, a minority of patients will develop life-threatening arrhythmias, conduction disturbances, or circulatory collapse .

Clinical Phenotypes

- Dilated Cardiomyopathy
- Fulminant Myocarditis
- Acute Coronary Syndrome
- Sudden Death

Dilated cardiomyopathy (DCM) phase

It remains uncertain why these patients develop chronic dilation. One proposed mechanism is based on a predisposing immunogenetic background that renders the individual more susceptible to a prolonged autoimmune response due to incomplete clearance of cardiac viral genomes or self-myocardial antigens.

Diagnosis

1)- ECG: Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes.

2)-CHEST X.RAY:

Reveal cardiomegaly, pulmonary vascular prominence, pulmonary edema, or pleural effusions.

3)-ECHOCARDIOGRAPHY:

Often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial effusion.

4)-Endomyocardial biopsy:

May be useful in identifying inflammatory cell infiltrates or myocyte damage.

5)-OTHER SUPPORTIVE BUT NONSPECIFIC TESTS INCLUDE:

- **WBC; often elevated.**
- **ESR increased.**
- **Troponins elevated in 1/3rd cases.**
- **CK (C**reatine kinase) **may be elevated.**
- **AST (**aspartate aminotransferase) **may be elevated.**

ACUTE MANAGEMENT

Overview — Because of the high risk of arrhythmias and hemodynamic compromise during the acute inflammatory phase of the disease, children with myocarditis who present with severely depressed ventricular function or rhythm disturbances should be cared for in a pediatric intensive care unit.
All patients require ongoing cardiorespiratory monitoring as the hemodynamic status of the patient may quickly deteriorate even if cardiac function is initially intact.

Therapy for pediatric myocarditis during the acute phase includes:

- Supportive care to maintain hemodynamic stability and adequate systemic perfusion.
- In cases of fulminant disease, this may necessitate the use of mechanical support of the circulation using extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD), followed by cardiac transplantation.

- Detection and treatment of arrhythmias.

- Immunomodulatory therapy.

Hemodynamic support

At presentation, infants and children with myocarditis usually have signs and symptoms of heart failure. Supportive care interventions depend upon the degree of symptoms:

- Initial supportive treatment consists of supplemental oxygen and careful fluid resuscitation.
- Children with mild symptoms can generally be managed with oral diuretics and after load-reducing agents (eg, angiotensin-converting enzyme inhibitors).
- Children with more severe symptoms (ie, decompensated heart failure or cardiogenic shock) may require intravenous inotropic support, mechanical ventilation, and even mechanical circulatory support .

Decompensated heart failure/cardiogenic shock

Severely affected patients are at risk for circulatory collapse. Medical intervention for these patients includes:

Intensive management of heart failure
– This includes intravenous diuretics and inotropic agents, such as milrinone, dopamine, and dobutamine.

Positive pressure ventilation

Positive pressure ventilation can improve cardiac function by reducing work of breathing, reducing left ventricular afterload, and increasing systemic oxygen levels.
Positive pressure ventilation can be provided noninvasively (eg, bilevel positive airway support) or via an endotracheal tube.
Intubation and sedation have the additional benefit of further reducing metabolic demand, which may be beneficial for patients with cardiogenic shock.

Mechanical support

Infants and children with severe circulatory compromise despite medical management may need temporary mechanical circulatory support using ECMO or VAD .

ECMO is used more frequently than VAD support for acute myocarditis in children .

Temporary mechanical circulatory support is used to allow time for recovery of cardiac function Less commonly, it serves as a bridge to transplantation .

In a report from the multicenter Extracorporeal Life Support Organization registry of ۲۵۵ pediatric patients with myocarditis supported with ECMO, survival to hospital discharge was ۶۱ percent .
Most survivors recovered cardiac function and were successfully separated from ECMO.
ECMO was used as a bridge to transplantation in only seven patients (۳ percent), of whom six survived to hospital discharge.
Among nonsurvivors in this cohort, ECMO support was withdrawn in ۷۰ percent, most of whom had multiple organ failure.

In another review of ۵۱۴ pediatric hospital admissions for acute myocarditis from the Pediatric Health Information System (PHIS) database, ۲۰ percent received ECMO or VAD support during the hospitalization, of whom ۱۶ percent underwent cardiac transplantation .

Of the remaining patients who required temporary circulatory support, ٢٤ percent died and the remaining patients (٦٠ percent) had recovery of cardiac function and survived to discharge after separation from VAD or ECMO support.

Patients who require mechanical support are more likely to have ventricular arrhythmia, bradyarrhythmia, and/or evidence of other organ dysfunction (eg, acute kidney injury, elevated transaminases) at the time of presentation compared with patients managed without mechanical support.

Arrhythmia management

Clinicians should maintain a high level of vigilance around monitoring for arrhythmias.

Loss of sinus rhythm may lead to acute deterioration or may exacerbate the symptoms of heart failure.

Arrhythmias are also a harbinger of severely depressed ventricular function and poor outcome.

In one series of ۸۵ pediatric patients hospitalized with myocarditis, ۳۸ (۴۵ percent) had clinically significant arrhythmias, with ventricular arrhythmias and complete heart block being the most common.

The presence of arrhythmias conferred an eightfold increase in risk of need for mechanical support, heart transplant, or death .

In a study using data from the PHIS database on ۲۰۱۴ children with myocarditis, patients with tachyarrhythmias had a ۲٫۳-fold increase in the odds of death and ۵۸ percent increase in length of stay compared with those without tachyarrhythmias .

Since most antiarrhythmic drugs have negative inotropic effects with potential to cause acute hemodynamic instability, these drugs should be used only when the expected benefit exceeds the risk.

Consultation with a pediatric cardiologist or a clinician with experience in managing arrhythmias in children is strongly advised.

Our approach is as follows:

- Supraventricular or ventricular arrhythmias associated with acute hemodynamic instability should be converted electrically without delay.

- Supraventricular arrhythmias, particularly when associated with a rapid ventricular response, may induce or aggravate heart failure. These arrhythmias should be converted promptly, either with drugs or with electrical cardioversion if medical therapy is unsuccessful.

An individualized approach is essential because the mechanisms of atrial arrhythmias in acute myocarditis are diverse (they may be automatic or reentrant in nature) and, thus, a single treatment strategy will not work for all patients. Electrical cardioversion and adenosine are generally less effective for terminating automatic atrial arrhythmias (eg, ectopic atrial ectopic tachycardia, focal atrial tachycardia) as compared with reentrant arrhythmias.

A limited attempt at vagal maneuvers (Valsalva) may be utilized in stable, cooperative patients but not in unstable patients. In these patients, rapidly moving to more advanced therapy is warranted and is discussed separately.

- High-grade ventricular ectopy should be treated cautiously with antiarrhythmic drugs.
- All antiarrhythmic drugs have significant side effects, and many have negative inotropic, vasodilatory, or proarrhythmic effects.
- Therefore, our choice of antiarrhythmic therapy is highly individualized based on patient characteristics.
- Lidocaine is our preferred agent for treatment of ventricular ectopy in this setting.

Although intravenous amiodarone is widely used to treat ventricular ectopy in adult sand is included as a first-line therapy in Pediatric Advanced Life Support algorithms, the \potential for serious adverse effects such as hypotension and atrioventricular block is considerable .

Thus, extreme caution should be used when administering this agent, particularly in young patients. This agent should be used only in collaboration with an experienced clinician.

- Complete heart block with compromised cardiac output is an indication for transvenous pacing. This conduction abnormality is often transient. Thus, use of a temporary pacemaker should be the first step.

Providing complete mechanical support of the circulation with ECMO or a VAD can belief saving in children with acute fulminant myocarditis and hemodynamically significant arrhythmias. Since many patients with fulminant disease recover completely if they can be supported through their acute illness, we use ECMO in the setting of a significant and persistent arrhythmia to allow myocardial recovery and safe pharmacologic therapy for the rhythm disturbance.

Anticoagulation

Practice varies with regard to anticoagulation in children with acute myocarditis. For most patients with mild myocarditis, anticoagulation to prevent venous thromboembolism is not routinely necessary unless there are other indications or additional risk factors (eg, obesity, oral contraceptive use).

However, patients with severe ventricular dysfunction are at increased risk for thrombus formation and anticoagulation with aspirin, unfractionated heparin, low molecular weight heparin, direct oral anticoagulant, or warfarin can be considered .

There is no standard approach. In our practice, we typically use unfractionated heparin during the acute phase while the patient is in the intensive care unit and then transition to aspirin once the clinical status has improved.
Aspirin is continued until ventricular function has improved (eg, left ventricular ejection fraction [LVEF] >۴۰ percent).

If thrombus is documented, we typically treat with low molecular weight heparin.

Immunomodulatory therapy

Data are limited and inconclusive as to whether intravenous immune globulin (IVIG) or glucocorticoids improve outcomes in pediatric myocarditis .

Nevertheless, IVIG has been used commonly because myocarditis is associated with considerable risk of mortality and morbidity and the risks associated with IVIG are usually small in comparison.

In multicenter observational studies in the United States from the mid-٢٠٠٠s to mid-٢٠١٠s, approximately ٧٠ percent of pediatric patients with myocarditis were treated with IVIG and ٢٠ to ٣٠ percent received glucocorticoids . Similar rates were reported in a nationwidestudy from Japan .

However, use of IVIG and glucocorticoids for children with myocarditis has become more common in the coronavirus disease ٢٠١٩ (COVID-١٩) era since these therapies are first-line treatments for patients with COVID-١٩-related multisystem inflammatory syndrome in children (MIS-C), which often presents similarly to acute myocarditis.

Intravenous immune globulin

For most children diagnosed with acute myocarditis, we suggest treatment with IVIG.

This applies to patients diagnosed based upon clinical findings, cardiac magnetic resonance imaging, or endomyocardial biopsy.

We feel that, given the considerable risks of death and morbidity associated with myocarditis, the potential side effects associated with IVIG are justified in this setting.

It is reasonable to omit IVIG therapy in patients who are not severely affected

The dosing for IVIG in this setting is ٢ g/kg administered in a single infusion over ٨ to ٢٤ hours.
In obese patients, the dose should be based upon ideal body weight.
For patients with significant cardiac dysfunction, if there is concern that the patient will not tolerate the volume load of the full dose in a single infusion, it can be given in divided doses over two days.

The use of IVIG to treat myocarditis was suggested by its efficacy in other immune-mediated diseases.

Randomized-controlled trial data of IVIG for the treatment of myocarditis are limited. A ٢٠٢٠ systematic review identified two small adult trials and one small pediatrictrial that were deemed to be at high risk of bias

In the pediatric trial, there was a trend toward improved transplant-free survival, but it did not reach statistical significance .

LVEF at hospital discharge was higher in the IVIG group compared with control .

Glucocorticoids

Use of glucocorticoids for the treatment of acute myocarditis is generally limited to patients who are refractory to IVIG and patients in whom myocarditis is associated with systemic autoimmune or inflammatory conditions (eg, COVID-١٩-relatedMIS-C, systemic lupus erythematosus).

Evidence remains inconclusive on the benefit of glucocorticoid therapy in patients with myocarditis.

In a meta-analysis of trials that included children and adults, mortality rates were similar in patients treated with and without glucocorticoids (relative risk ۰/۹۳, ۹۵% CI۰/۷۰-۱/۲۴)

. At one to three months follow-up, the group that received steroids had higher LVEF (mean difference ۷/۴ percent, ۹۵% CI ۴/۹-۹/۸).

Observational studies evaluating the efficacy of glucocorticoids in acute myocarditis have reached variable conclusions .
One study reported that combination therapy with IVIG plus glucocorticoids is associated with recovery of ventricular function and high rates of transplant-free survival .
Another study failed to detect a meaningful difference in mortality or cardiovascular complications in patients treated with or without glucocorticoids

Antiviral therapies

Although viral infection is the most common identified cause of myocarditis in children, the efficacy of antiviral therapy for myocarditis is uncertain. Thus, antiviral therapy is not a routine component of treatment for myocarditis in children.

Considerations and evidence regarding antiviral therapy for specific viral infections are discussed in separate topics:

- Enterovirus
- Adenovirus
- Parvovirus B۱۹
- Cytomegalovirus
- Human herpes ۶
- Severe acute respiratory syndrome coronavirus ۲ (SARS-CoV-۲)

Limited data suggest potential benefit of interferon beta therapy in adult patients with chronic dilated cardiomyopathy (DCM) and confirmed myocardial viral infection .However, similar findings have not been reported in children.

CHRONIC MANAGEMENT

Chronic heart disease

For patients who progress from acute myocarditis to chronic heart failure, diuretics, angiotensin-converting enzyme inhibitors, digoxin, beta blockers, and aldosterone inhibitors (ie, spironolactone) are well-accepted therapies and are discussed in greater detail separately.

Recurrent disease

Some patients may relapse after the first episode, sometimes many years later . Relapses should be managed in a similar manner to the initial episode

ROUTINE FOLLOW-UP ISSUES

Activity

Although data are limited, experts in the field suggest that strenuous physical activity and exercise be restricted in patients with complete resolution of myocarditis for at least six months after the onset of the disease
.

Preparticipation screening should be performed prior to resuming athletic competition. This may entail exercise testing inpatients after the acute phase of their disease.

Patients who continue to have impaired ventricular function may benefit from exercise rehabilitation.

Immunization

Live-virus vaccination may have diminished immunogenicity when given to a child who has recently received intravenous immune globulin (IVIG). Based on the recommendations from the American Academy of Pediatrics, we suggest that immunization with live vaccine be delayed for ١١ months for children who receive IVIG for myocarditis

.For patients undergoing heart transplant, live vaccines should be given prior to transplantation, despite concerns of decreased efficacy, given that live vaccines are contraindicated with the administration of immunosuppressive therapy following transplantation.

PROGNOSIS

Studies examining outcomes in children with myocarditis are limited by small numbers of patients, limited duration of follow-up, variability in case definition (biopsy confirmed versus clinical diagnosis), and inclusion of patients with other diagnoses (eg, dilated cardiomyopathy [DCM]).
Based on the available evidence, it appears that the risk of morbidity and mortality is greatest during the acute illness.
Most survivors recover ventricular function without long-term cardiac impairment (including arrhythmias), though a small subset develop DCM .

Mortality

Reported mortality rates during the acute illness for children with myocarditis range from ۶ to ۱۴ percent.

Late deaths are uncommon, occurring in <۵ percent of patients .

Most late deaths are due to persistent ventricular dysfunction, heart failure, or complications following heart transplantation .

Factors associated with increased risk of death include:

- Fulminant presentation
- Severely depressed left ventricular function (eg, left ventricular ejection fraction[LVEF] <٣٠ percent or fractional shortening Z-score <-٢)
- Need for mechanical support (extracorporeal membrane oxygenation [ECMO] or ventricular assist device [VAD])
- Need for intravenous inotropic therapy (eg, milrinone, dopamine, and dobutamine)
- Tachyarrhythmias
- Peak B-type natriuretic peptide level >١٠’٠٠٠ pg/mL

Heart transplantation

Approximately ٥ to ٢٠ percent of children with acute myocarditis require heart transplantation .
Risk factors are similar to the mortality risk factors listed above.
Severely affected patients often require mechanical support (ECMO or VAD) as a bridge to transplant.

It is unclear if patients with myocarditis are at risk for poor outcome following transplantation compared with children who undergo cardiac transplantation for other reasons (eg, DCM, congenital heart disease [CHD]).

Compared with children with Idiopathic DCM, patients with myocarditis may have more severe heart failure and require a greater degree of hemodynamic support at the time of transplant (including inotropes and in some cases, mechanical support)

In a registry study that evaluated transplant outcomes in ٢٢١ children with myocarditis and ١٥٨٣ children with idiopathic DCM, after adjustment for severity of illness, myocarditis was not independently associated with waitlist mortality or post-transplant graft loss . Another registry study evaluating transplant outcomes in ٧٠٩ patients with myocarditis and ١٦٣١ patients with CHD found that graft survival varied with age.

Among patients with myocarditis, median graft survival was ۱۴٫۱ years for school-age children(۶ to ۱۲ years old) and ۶٫۹ years for adolescents (۱۳ to ۱۸ years old). Among patients with CHD, median graft survival was ۹ years for school-age children and ۷٫۴ years for adolescents

Long-term morbidity

Though most children ultimately have complete or partial recovery of left ventricular function, a subset of patients develop chronic DCM .
Recovery of cardiac function tends to be gradual, occurring over months to years.
Most patients have evidence of ongoing left ventricular dysfunction at the time of discharge from the hospital.

In a retrospective multicenter study of ۱۷۱ children with acute myocarditis diagnosed from ۲۰۰۸ to ۲۰۱۲, ۵۵ percent were discharged on heart failure medications and ۱۶ percent were readmitted to the hospital for heart failure symptoms during the first year following discharge .
In a report of ۳۷۲ children with myocarditis, ۵۳ percent had normal echocardiographic parameters at three years after presentation .

In another study of ٧٠ children with myocarditis who were treated with immunomodulatory therapy, the rate of complete recovery of ventricular function at a median follow-up of six years was ٧٠ percent .
In a small series of ٣۶ children with histologically confirmed myocarditis with median follow-up of ١٩ months, approximately one-half of patients recovered normal left ventricular function within three months .
None of the survivors reported cardiac symptoms or restrictions in physical activity, and none required antiarrhythmic treatment.
Patients who do not fully recover cardiac function may develop DCM.
DCM is preceded by myocarditis in ٢٧ to ۴٠ percent of cases in children

Comparison of Multisystem Inflammatory Syndrome in Children–Related Myocarditis, Classic Viral Myocarditis, and COVID-19 Vaccine-Related Myocarditis in Children

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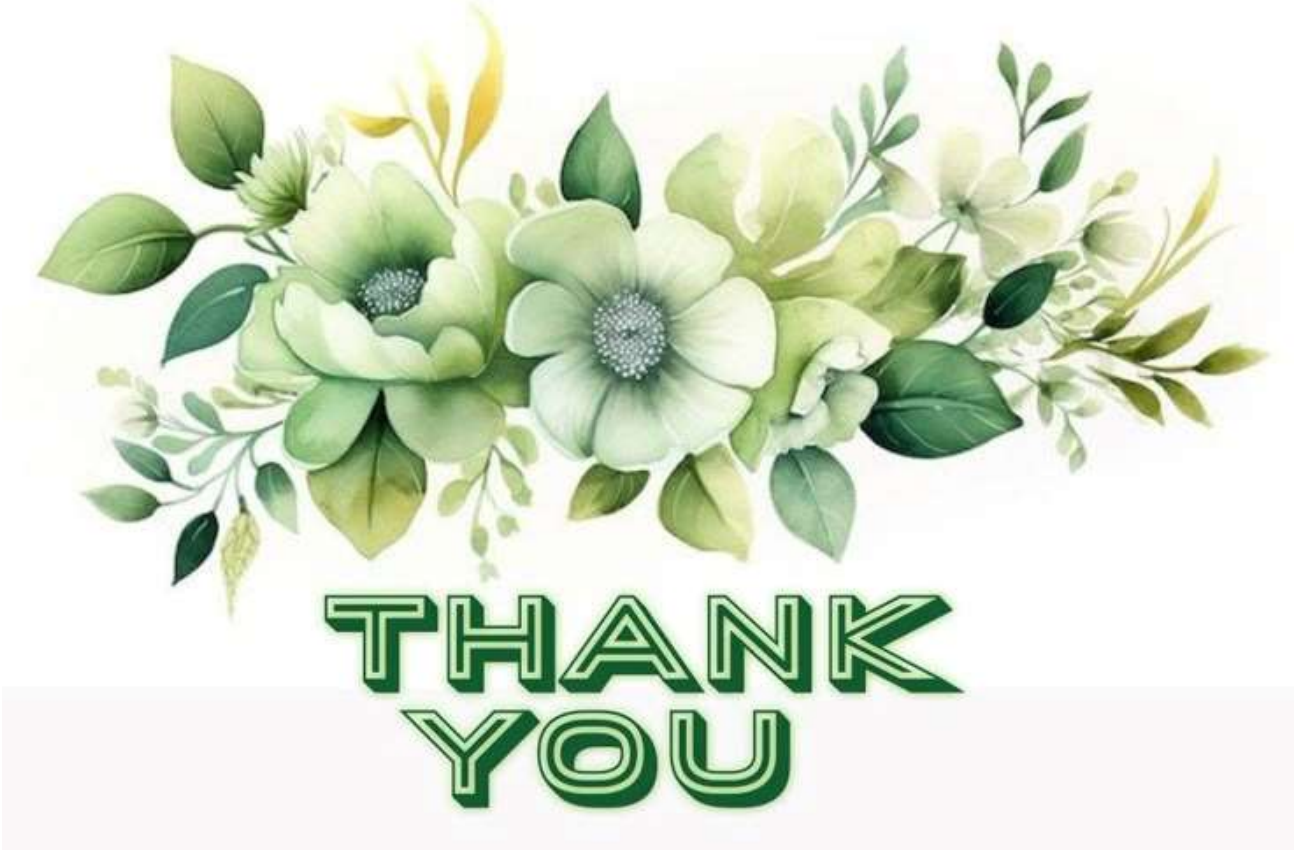
Conclusions

Compared with classic myocarditis, those with MIS-C myocarditis had better clinical outcomes, including rapid recovery of cardiac function. Patients with vaccine-related myocarditis had prompt resolution of symptoms and improvement of cardiac function.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