PEDIATRIC EMERGENCY MEDICINE REPORTS

Practical, Evidence-Based Reviews in Pediatric Emergency Care

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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Dietrich (editor), Dr. Skrainka (CME question reviewer), Dr. Heaton (author), Dr. Keaveny (author, Dr. Marco (peer reviewer), Ms. Coplin (executive editor), and Ms. Kimball (managing editor) report no relationships with companies related to the field of study covered by this CME activity.

AHC Media

Pediatric Myocarditis

Myocarditis is defined by the World Health Organization/International Society and Federation of Cardiology as "an inflammatory disease of the myocardium and is diagnosed by established histological, immunological, and immunohistochemical criteria." When myocarditis is associated with cardiac dysfunction, it is termed inflammatory cardiomyopathy.[1] *While myocarditis most often has an infectious etiology, other possible causes include autoimmune disease, toxins, and hypersensitivity reactions.*[2] *It is most often due to a viral infection in developed countries. In Central and South America, myocarditis is commonly caused by* Trypanosoma cruzi *infection.*[2]

Myocarditis poses an interesting dilemma for the emergency physician. Classically, patients present with heart failure (HF) a few weeks after a viral illness; however, many patients do not present with the classic symptoms.[2] *The diagnosis can be difficult secondary to a variety of presentations which can range from an asymptomatic, subclinical presentation to acute fulminant myocarditis characterized by cardiovascular collapse and even sudden death.*[3,4] *In addition, symptomatic patients often present with signs and symptoms that have a very broad differential diagnosis including predominantly respiratory or gastrointestinal symptoms.*

Myocarditis is associated with dilated cardiomyopathy and can lead to significant morbidity and mortality.[3,4,5] *Just as the clinical presentation can be quite varied, so too can the prognosis. Therefore, the emergency physician must have a high index of suspicion for this very difficult diagnosis and potentially deadly disease entity.*

— Ann M. Dietrich, MD, FAAP, FACEP, Editor

Epidemiology

Myocarditis can at times be asymptomatic and has a varied presentation; consequentially, it often goes undiagnosed and its true incidence is unknown.[6] A chart review of patients seen in a pediatric emergency department in Taiwan found that 27 of the 224,435 patients seen in the study period were diagnosed with myocarditis, making the incidence at that institution's emergency department 1.2 cases per 10,000 visits, with the majority of those affected being male.[7] A nationwide study by Saji et al predicted the annual incidence in Japan to be 0.24 cases per 100,000 population.[8]

A U.S. study by Ghelani et al identified 514 pediatric patients with acute myocarditis from April 2006 to March 2011 using the Pediatric Health Information System database and found a bimodal age distribution with a predominance of males (64% overall), especially in the > 12 year old age group where males accounted for 80.9%. Whites accounted for 41.4%, blacks for 22.4%, and Hispanics for 17.7% of the study population.[3]

During the recent influenza A/H1N1 pandemic, myocarditis was a

EXECUTIVE SUMMARY

- Although there are a multitude of infectious and noninfectious causes of myocarditis, the most common etiology in the United States is viral.
- Viral myocarditis can be described in three distinct phases: the viral phase, the autoimmune phase, and dilated cardiomyopathy.
- Myocarditis can be difficult to diagnose because patients present with a wide variety of symptoms and can have very non-specific complaints. Children can present with predominantly respiratory or gastrointestinal symptoms and may have no cardiac complaints.
- An electrocardiogram should be performed in all patients with clinically suspected myocarditis
- Laboratory tests recommended include troponin, brain natriuretic peptide, C-reactive protein, erythrocyte sedimentation rate, electrolytes, glucose, urea and creatinine for renal function, hepatic transaminases, thyroid hormone levels, and a complete blood count.
- Other tests used in diagnosis include chest radiography, echocardiography, cardiac magnetic resonance imaging, nuclear cardiac imaging, and endomyocardial biopsy.
- For patients diagnosed with myocarditis, limitation of activity is suggested. The primary treatment for myocarditis is supportive therapy.
- There is potential for complete recovery from myocarditis, but the diagnosis is associated with high rates of transplantation and mortality,

frequent complication worldwide. Often, pediatric patients requiring admission to pediatric ICUs had associated myocarditis, which also put these children at higher risk for death.[9,10,11,12]

Etiology

Although there are a multitude of infectious and noninfectious causes of myocarditis, the most common etiology in the United States is viral.[6] Common viral pathogens associated with myocarditis include enteroviruses such as coxsackievirus, adenovirus, parvovirus B19, human herpes virus 6, Epstein-Barr virus, hepatitis C virus, and influenza.[4,13,14] There has been a trend over the past 2 decades from enteroviruses and adenoviruses as the primary cause to parvovirus and human herpesvirus 6 (*see Figure 1*).[2] Additionally, cytomegalovirus, measles, mumps, herpes zoster, and mycoplasma pneumonia all have been identified as less common infectious etiologies of myocarditis.[8] There are several less common non-infectious etiologies of myocarditis as well including autoimmune diseases, drug reactions, and hypersensitivity reactions. Table 1 reviews the various infectious and non-infectious etiologies of myocarditis.

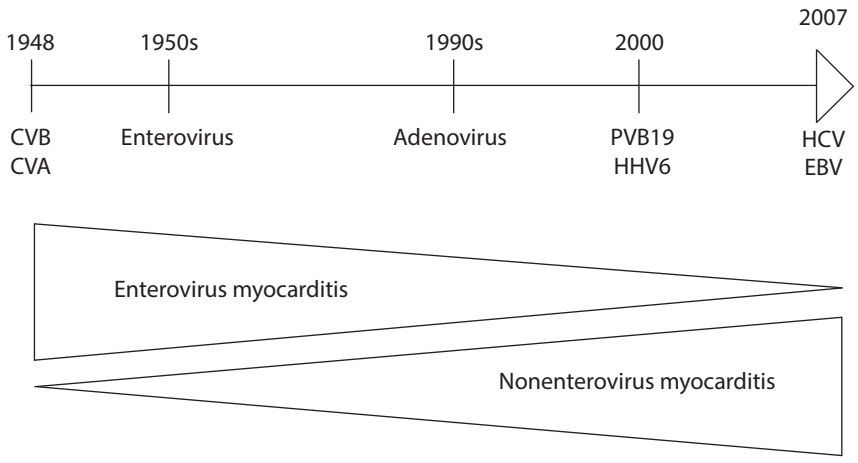
Pathophysiology

The pathogenesis of myocarditis is poorly understood due to the complex nature of the disease and its various etiologies (*see Figure 2*). Most knowledge is based on animal models of coxsackie and adenoviral infections.[18] Viral myocarditis can be described in three distinct phases: the viral phase, the autoimmune phase, and dilated cardiomyopathy.[15]

Phase 1 – The Viral Phase. Phase 1 commences with the entry of the virus. Coxsackievirus and adenovirus enter the cardiac myocyte via a common receptor, the coxsackie adenoviral receptor (CAR).[16] Lysis of the cardiomyocyte then triggers the innate immune response.[17] Cardiac myocyte injury is mediated by both the direct viral effect as well as the immune response.[18] Most patients recover from phase 1 without entering the second phase.[17] However, if the immune system does not down-regulate once viral proliferation is controlled, phase 2, autoimmune disease, results.[15]

Phase 2 – The Autoimmune Phase. If the immune system is not down regulated, the host's tissue is targeted by T cells, cytokine activation, and cross-reacting antibodies.[15] This is the autoimmune phase. If the virus is not cleared or the inflammatory process continues, the patient

Figure 1. Timeline of Myocarditis Etiology Over the Years[14]



CVA = coxsackievirus A; CVB = coxsackievirus B; EBV = Epstein-Barr virus; HCV = hepatitis C virus; HHV6 = human herpesvirus 6; PVB19 = parvovirus B19.

Reprinted with permission from: Schultz JC, Hilliard AA, Cooper LT Jr, et al. Diagnosis and treatment of viral myocarditis. *Mayo Clin Proc* 2009;84:1001-1009.

Table 1. Etiology of Myocarditis[2,23,24]

Causes	Examples	
Infectious	Viral	RNA viruses: enteroviruses (e.g., coxsackieviruses A and B), echoviruses, HCV, HIV, influenza A and B viruses, polioviruses, RSV, measles virus, mumps virus, rubella virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus DNA viruses: adenoviruses, PVB19, herpesviruses (HSV, VZV, CMV, EBV, HHV6), pox viruses (variola virus, vaccinia virus)
	Bacterial	Chlamydia, *Corynebacterium diphtheria*, legionella, *Mycobacterium tuberculosis*, mycoplasma, staphylococcus, streptococcus A, *Streptococcus pneumoniae*, meningococcus, gonococcus, salmonella, *Haemophilus influenzae*, Brucella
	Fungal	Actinomyces, aspergillus, candida, Cryptococcus, Blastomyces, Coccidioides, Histoplasma, Mucormycoses, Nocardia, Sporothrix
	Helminthic	*Echinococcus granulosus*, *Trichinella spiralis*, *Taenia solium*
	Protozoal	*Toxoplasma gondii*, *Trypanosoma cruzi*, *Entamoeba*, *Leishmania*
	Rickettsial	*Coxiella burnetii*, *Rickettsia typhi*, *Rickettsia rickettsii*, *Orientia tsutsugamushi*
	Spirochetal	*Borrelia burgdorferi*, leptospira, *Treponema pallidum*
Autoimmune	giant cell myocarditis, lymphofollicular myocarditis celiac disease, Churg-Strauss syndrome, Crohn's disease, dermatomyositis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematosus, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis, inflammatory bowel disease, polymyositis, myasthenia gravis, diabetes mellitus, thyrotoxicosis, granulomatosis with polyangiitis (formerly Wegener's granulomatosis), rheumatic heart disease	
Hypersensitivity	Tetanus toxoid, smallpox vaccine, serum sickness Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop diuretics, thiazide diuretics, methyldopa, tricyclic antidepressants, colchicine, isoniazid, lidocaine, phenytoin, phenylbutazone	
Toxic	Drugs	amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, interleukin-2, trastuzumab, clozapine, phenytoin
	Heavy metals	copper, iron, lead
	Other toxins	scorpion sting, snake bite, spider bite, bee sting, wasp sting, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide, pheochromocytoma, thyrotoxicosis, radiation, electric shock
Other	arsenic, copper, iron, radiotherapy, thyrotoxicosis	

Abbreviations: CMV = human cytomegalovirus, EBV = Epstein-Barr virus, HCV = hepatitis C virus, HHV6 = human herpesvirus 6, HIV = human immunodeficiency virus, HSV = herpes simplex virus, PVB19 = parvovirus B19, RSV = respiratory syncytial virus, VZV = varicella-zoster virus

may progress to phase 3.[17]

Phase 3 – Dilated Cardiomyopathy. Phase 3 is characterized by the development of dilated cardiomyopathy (DCM). This can occur in patients in whom the virus is not cleared or the inflammatory process is not appropriately down regulated. Persistence of the inflammatory process can lead to remodeling and subsequent development of DCM.[19]

Clinical Features

History. Myocarditis can be difficult to diagnose because patients present with a wide variety of symptoms and can have very non-specific complaints. Children can present with predominantly respiratory or gastrointestinal symptoms and may have no cardiac complaints. Older children are more likely than younger children to present with

cardiac symptoms.[4] See Table 2 for signs and symptoms of myocarditis.

Physical exam. Physical exam findings consistent with myocarditis are also varied. Fever, tachycardia, bradycardia, hypotension, tachypnea, respiratory distress, lethargy, gallop, murmur, hepatomegaly, and poor perfusion are physical exam findings that may be present in patients with myocarditis, all of which are non-specific. Infants often present with hypoxia (SpO_2 < 95%) and poor perfusion.[4] Children aged 1-5 years are often febrile and tachycardic; hepatomegaly is present in more than half of this age group. Poor perfusion and lethargy are again common in these children. Hypotension, lethargy, and poor perfusion are the most common exam findings in children over the age of 6 years. Twenty-one percent of this age group had a gallop or murmur and 42% had hepatomegaly.[4] Table 3 reviews physical exam findings seen in myocarditis.

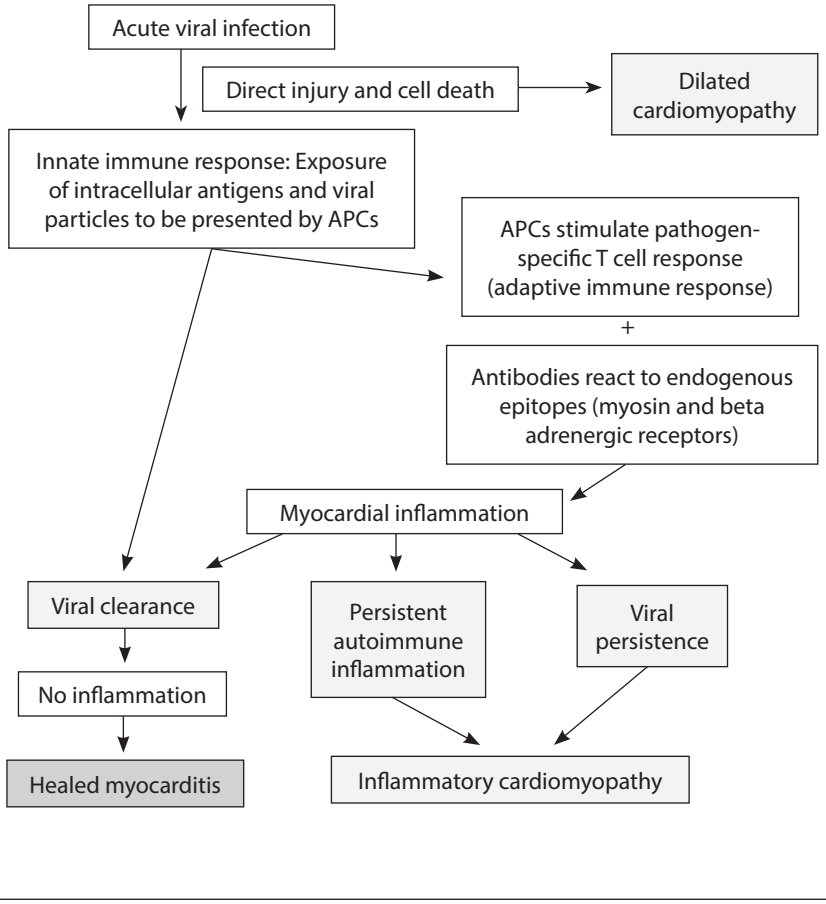
The Canadian Cardiovascular Society (CCS) released recommendations based on a consensus panel regarding commonly seen symptoms in pediatric myocarditis. According to the CCS, "myocarditis should always be considered in the differential diagnosis of children who present with a viral prodrome and nonspecific respiratory or abdominal symptoms associated with tachycardia, hypotension, or cardiac rhythm abnormalities, even in the absence of cardiomegaly on chest x-ray."[20]

Diagnostic Evaluation

Electrocardiogram (ECG). An electrocardiogram should be performed in all patients with clinically suspected myocarditis. There is no single finding that is specific for myocarditis, however, an abnormality on ECG is frequently found.

Common abnormalities seen on ECG include sinus tachycardia, heart block, ST or T-wave abnormalities, axis deviation, decreased voltage, and arrhythmias including ventricular tachycardia.[4,21,22] Transplant-free survival is associated with the absence of ST changes.[13] See Table 4 for ECG changes seen in myocarditis and Figure 3 for ECG findings in myocarditis.

Figure 2. Pathogenesis of Myocarditis[17]



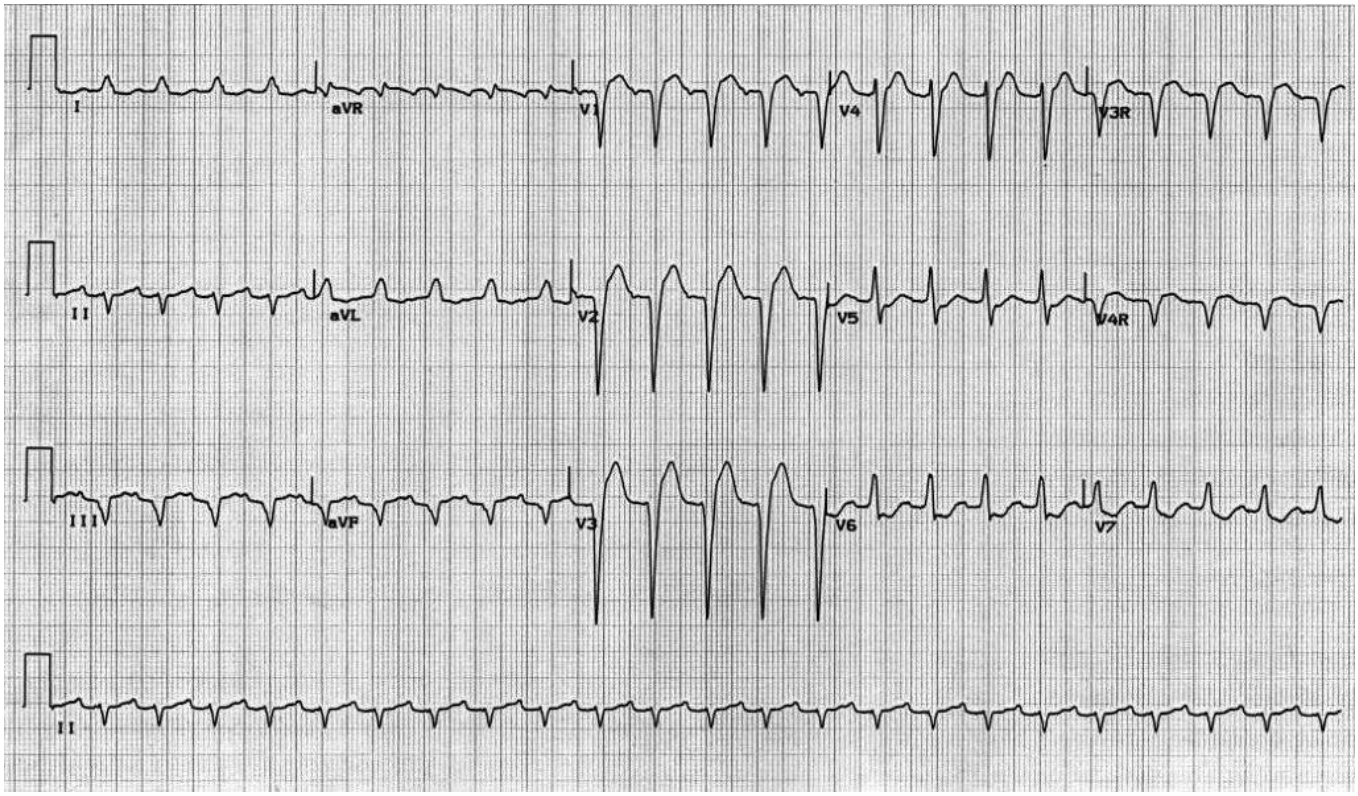
Reprinted from: Shauer A, Gotsman I, Keren A, et al. Acute viral myocarditis: Current concepts in diagnosis and treatment. *Isr Med Assoc J* 2013;15:180-185.

Table 2. Signs and Symptoms of Myocarditis

Signs, Symptoms	Age
Hypoperfusion	Most common symptom in infants and children ages 1-5 years
Fever	All ages
Poor feeding	All ages
Cardiopulmonary collapse	Most common in infants, but can be seen in all ages
GI symptoms, including vomiting	All ages
Chest pain	Uncommon complaint

The European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial

Figure 3. ECG Findings in Myocarditis



ECG with low voltage in the limb leads and an infarct pattern

*ECG provided by Bryan Cannon, M.D., Mayo Clinic, Rochester, MN

Diseases recommends a 12-lead ECG be performed for all patients with suspected myocarditis.[23]

Laboratory evaluation. *Troponin.* Troponin should be obtained whenever there is clinical suspicion for myocarditis. Often, troponin is elevated in these patients.[4,21] The sensitivity depends on the cutoff value. A study by Eisenberg et al found the sensitivity of cardiac troponin T to be 100% for myocarditis using > 0.01 ng/mL as a positive test.[21] Shu-Ling et al found the sensitivity of troponin to be 81.5%; > 0.10 ng/mL was considered a positive troponin in this study.[4] The ESC recommends troponin be assessed in all patients with clinically suspected myocarditis.[23]

Brain natriuretic peptide (BNP). BNP can also be a helpful laboratory test to obtain in patients with suspected myocarditis and in patients who present with heart failure. Molina et al found that serum BNP was elevated in 100% of patients with Parvovirus B19 myocarditis who had it drawn.[13] According to the CCS, "BNP or NT-proBNP levels are useful in distinguishing heart failure from respiratory or other noncardiac disease and should be used as a confirmatory test in the acute evaluation of pediatric heart failure."[20]

Inflammatory/Infectious Markers. Patients with myocarditis often have elevated white blood cell count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); however, the absence of elevation of these inflammatory markers does not definitively exclude myocarditis.[2,24] The ESC recommends ESR and CRP be assessed in all patients with clinically suspected myocarditis.[23]

Other Laboratory Tests. The CCS recommends including additional initial laboratory tests such as electrolytes, glucose, urea and creatinine for renal function, hepatic transaminases, thyroid hormone levels, and a complete blood count in children with suspected myocarditis. Reassessment with repeat labs to assess clinical course is appropriate.[20]

Chest Radiography. While often normal in patients with myocarditis, abnormal findings can suggest the diagnosis. Concerning chest x-ray findings include cardiomegaly, pulmonary congestion, and pleural effusions.[4,13]

Shu-Ling et al found that 60% of those children diagnosed with acute myocarditis in their series who had a chest x-ray performed had an abnormal finding, the most common being cardiomegaly, which occurred in 42.9%. Pulmonary congestion was observed in 25.7% and one case had a pleural effusion.[4] Molina et al found that chest radiography demonstrated cardiomegaly in 89% and pleural effusions in 47% of patients with parvovirus B19 myocarditis.[13]

Table 3. Physical Exam Findings in Myocarditis

Fever
Tachycardia/bradycardia
Hypotension, poor perfusion
Respiratory distress
Lethargy
Abnormal heart sounds: gallop, murmur
Hepatomegaly
Hypoxia
Peripheral edema
Cyanosis
GI symptoms: nausea, vomiting, diarrhea, abdominal pain
Additional cardiac symptoms: heart failure, arrhythmia, cardiogenic shock

Table 4. ECG Findings in Myocarditis

Sinus tachycardia
Heart block
ST or T wave abnormalities
Arrhythmias
Axis deviation
Decreased voltage

According to the CCS, "Chest radiography is indicated as a first-line investigation in children with suspected heart failure."[20]

Echocardiography. Echocardiography is an important part of the assessment of patients with suspected myocarditis. Frequently, moderate-to-severe ventricular dysfunction with depressed ejection fraction is seen on echocardiogram as well as left ventricular end diastolic dysfunction.[13] Additional findings include mitral valve regurgitation, pericardial effusion, and ventricular wall thickening.[8,22] The ESC recommends transthoracic echocardiogram on all patients with suspected myocarditis with repeat imaging during hospitalization if there is deterioration in hemodynamic status.[23]

According to the CCS, "all patients with symptoms consistent with heart failure should undergo transthoracic echocardiography in a pediatric cardiology facility at, or as soon as possible after, initial presentation."

The CCS also recommends "a diagnosis of acute myocarditis should be considered in all children, regardless of age, who present with new onset heart failure without a history of decreased functional capacity, and specifically if echocardiographic ventricular dilation is less than expected for the degree of systolic dysfunction and clinical severity."[20]

Cardiac magnetic resonance imaging (CMRI). Cardiac MRI is a useful adjunct in the diagnosis of myocarditis. Recently, it has been utilized more frequently across the country and may demonstrate benefit over endomyocardial biopsy.[3] CMRI can assess cardiac function, morphology, and tissue pathology. Left ventricular function, presence or absence of pericardial effusion, and wall thickness can all be assessed. Regional edema can be evaluated, though the sensitivity of edema on CMRI may be limited in cases of myocarditis that are less severe. Signs of tissue inflammation such as hyperemia and capillary leak can be visualized as early gadolinium enhancement. Signs of myocardial injury such as necrosis and fibrosis can be visualized as late gadolinium enhancement.[25] Indications for CMRI (*see Table 5*) and proposed CMRI diagnostic criteria for myocarditis (*see Table 6*) have been set forth by The International Consensus Group on CMR Diagnosis of Myocarditis.[25]

Table 5. Indications for Cardiac MRI in Patients with Suspected Myocarditis[25]

Symptoms Suggestive of Myocarditis (new or persisting)	*plus*	Evidence for Myocardial Injury (recent or ongoing)	*plus*	Suspected Viral Etiology
Dyspnea *or* orthopnea *or* palpitations *or* effort intolerance/malaise *or* chest pain		Ventricular dysfunction *or* new or persisting ECG abnormalities *or* elevated troponin		History of recent systemic viral disease or previous myocarditis *or* absence of risk factors for coronary artery disease or age of < 35 years *or* symptoms not explained by coronary stenosis on coronary angiogram ***or*** recent negative ischemic stress test

Adapted from: Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC white paper. *J Am Coll Cardiol* 2009;53:1475-1487.

The ESC recommends CMRI be considered prior to endomyocardial biopsy (EMB) in clinically stable patients, but that it does not replace EMB in the diagnosis of myocarditis and should not delay EMB in life-threatening presentations.[23]

According to the CCS, "CMRI might assist in the clinical diagnosis of myocarditis, and might provide additional information in cardiomyopathies by tissue and scar characterization. The prognostic value of CMRI findings is not yet known."[20]

Nuclear Cardiac Imaging. Currently, nuclear imaging for the diagnosis of myocarditis is not commonplace and not a routine part of the workup for suspected myocarditis. Nuclear imaging has limited availability and carries the risk of radiation exposure.

There are several nuclear medicine tests that can be performed, including thallium (TI)-201 myocardial scintigraphy, iodine-123 metaiodobenzylguanidine myocardial scintigraphy, technetium-99m pyrophosphate scanning, and gallium-67 scintigraphy. Each has various sensitivities when used in the assessment of myocarditis.[8]

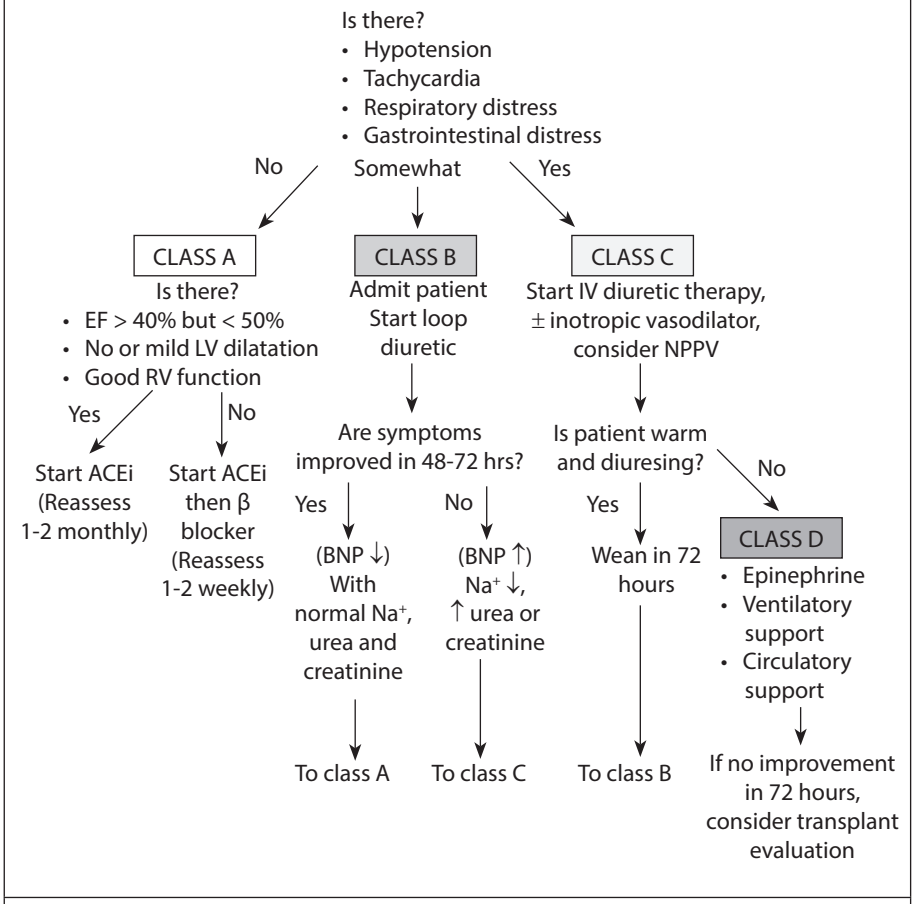
A small study out of Poland by Ziółkowska et al studied the usefulness of scintigraphy with 99-labeled monoclonal antigranulocyte antibody in the diagnosis of myocarditis. Eleven children with suspected myocarditis were evaluated, all of whom underwent scintigraphy. Of the eleven, one had a negative result; the remaining 10 had a positive result. Scintigraphy results were compared with EMB. The patient with negative scintigraphy had evidence of myocarditis on EMB. Of the 10 patients with positive scintigraphy, nine underwent EMB. Of those nine, eight had evidence of myocarditis on EMB while one had a negative EMB.[26]

Endomyocardial biopsy (EMB). Endomyocardial biopsies as a diagnostic necessity have significantly decreased.[3] When performed, suspected findings include: inflammatory cell infiltration, myocardial degeneration, myocardial necrosis, myocardial hypertrophy, interstitial edema, fibrosis, and eosinophil infiltration.[8]

According to the American Heart Association, the American College of Cardiology, and the European Society of Cardiology, "EMB is reasonable in the setting of unexplained cardiomyopathy in children."[28] Further, the Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines state, "Routine endomyocardial biopsy is not recommended in cases of new-onset heart failure. Endomyocardial biopsy should be considered in patients with rapidly progressive clinical HF or ventricular dysfunction, despite appropriate medical therapy. Endomyocardial biopsy also should be considered in patients suspected of having myocardial infiltrative processes, such as sarcoidosis or amyloidosis, or in patients with malignant arrhythmias out of proportion to left ventricular (LV) dysfunction, where sarcoidosis and giant cell myocarditis are considerations."[27] The CCS position on EMB states that biopsy should be undertaken in those where confirming the clinical diagnosis of myocarditis will have an effect on the patient's treatment. "EMB is not recommended in infants weighing less than 10 kg, or in patients who are hemodynamically unstable."[20] Therefore, indications for EMB in children include fulminant HF, acute unexplained HF, unexplained arrhythmias, and idiopathic forms of DCM.[28] Criteria for diagnostic classification of myocarditis does include endomyocardial biopsy (*see Table 7*).[19]

Viral Pathogens. Viral infection is a common etiology of pediatric

Figure 4. Algorithm for Heart Failure Management[20]



Reprinted with permission from: Kantor PF, Lougheed J, Dancea A, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol* 2013;29:1535-1552.

myocarditis. Methods of identifying viruses include antibody titer, viral culture and isolation, and detection of viral genome; however, the ESC does not recommend routine viral serology testing.[8,23]

Differential Diagnosis

Due to the varied and oftentimes non-specific presentation of myocarditis, the differential diagnosis is broad and there is potential for misdiagnosis. As noted previously, children often present with respiratory and/or gastrointestinal symptoms. Several different cardiovascular syndromes have been associated with myocarditis in the pediatric population as well, including sudden death, arrhythmias, chest pain/infarction, and acute heart failure with a dilated cardiomyopathy phenotype.[2] Therefore, the differential must include other causes of respiratory tract infection, gastrointestinal illness, arrhythmias, infarction and other potential causes of heart failure.

Table 6. Lake Louise Consensus Criteria for Diagnosis of Myocarditis by Cardiac MRI[25]

CMR findings are consistent with myocardial inflammation if two or more of the following are present:

1. Myocardial edema
   - increased signal (regional or global) in T2-weighted images
2. Early gadolinium enhancement
   - increased global myocardial early gadolinium
3. Late gadolinium enhancement
   - one or more focal lesions with late gadolinium enhancement

A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if:

- Criterion 3 is present

A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended, if:

- None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation
- One of the criteria is present

The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis

Adapted from: Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC white paper. *J Am Coll Cardiol* 2009;53:1475-1487.

Table 7. Diagnostic Criteria for Myocarditis[19]

Criteria		Histological Confirmation	Biomarker, ECG, or Imaging Abnormalities Consistent with Myocarditis
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury without cardiovascular symptoms and one or more 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	Absent	Required
Probable acute myocarditis	In the clinical context of possible myocardial injury with cardiovascular symptoms and one or more 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	Absent	Required
Definite myocarditis	Histological or immunohistological evidence of myocarditis	Required	Not Required

ECG = electrocardiogram

Adapted from: Sagar S, Liu PP, Cooper LT Jr. Myocarditis. *Lancet* 2012;379:738-747.

Table 8. ESC Recommendations on the Use of Immunosuppression in Myocarditis[25]

Immunosuppression should be started only after ruling out active infection on EMB by PCR.
Based on experience with non-cardiac autoimmune disease, the task group recommends consideration of immunosuppression in proven autoimmune (e.g., infection-negative) forms of myocarditis, with no contraindications to immunosuppression, including giant cell myocarditis, cardiac sarcoidosis, and myocarditis associated with known extra-cardiac autoimmune disease.
Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia and in some forms of infection-negative eosinophilic or toxic myocarditis with heart failure and/or arrhythmia.
Immunosuppression may be considered, on an individual basis, in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression.
Follow-up EMB may be required to guide the intensity and the length of immunosuppression.

Adapted from: Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC white paper. *J Am Coll Cardiol* 2009;53:1475-1487.

Management

Limitation of Activity. For patients diagnosed with myocarditis, limitation of activity is suggested. Recommendations from the 2005 Bethesda Conference include athletes with probable or definite myocarditis refrain from training or competition for approximately 6 months and may return to activity if follow-up assessments indicate normalization of left ventricular function, wall motion, cardiac dimensions, inflammatory markers and ECG, and absence of arrhythmias.[29] The ESC Working group has similar recommendations, but includes all patients thought to have myocarditis. The recommendation from the ESC is restriction of physical activity during the acute phase of myocarditis for a period of at least 6 months.[23]

Conventional Medical Management. The primary treatment for myocarditis is supportive therapy.[2,20]

Heart failure treatment. Heart failure should be treated according to established guidelines and can include diuretic therapy, ACE inhibition, beta blockade, and aldosterone antagonism.[2,17,20,27] Nitrates are uncommonly used for the treatment of heart failure in children. They may have a role in the treatment of acute systolic dysfunction in children with associated hypertension.[20] For patients presenting with cardiogenic shock or those who decompensate despite medical management, inotropes and mechanical ventilation or circulatory support may be employed.[2,17,20,27] Figure 4 reviews heart failure management.[20]

Use of vasopressors and inotropes for cardiovascular support is associated with increased risk of death and increased chance of transplantation, often due to the severe nature of these cases.[3]

Heart Block and Arrhythmias. Temporary pacing therapy should be instituted in patients with symptomatic second-degree or complete heart block. Permanent pacemaker placement is required in those patients with persistent complete block. An implantable cardiac defibrillator (ICD) should be inserted in patients who have had a ventricular fibrillation arrest or symptomatic ventricular tachycardia.[24] Because there is potential for significant improvement in left ventricular function, ICD implantation should not occur routinely during the acute episode of myocarditis.[23,24] An exception to this is patients who have second- or third-degree heart block or ventricular arrhythmia in the setting of sarcoidosis or giant cell myocarditis. Early pacemaker or ICD implantation may be considered in these patients because of the poorer prognosis.[24] The ESC recommends that arrhythmias outside the acute phase be managed according to their current guidelines.[23]

Immunomodulation. *Antiviral Therapy.* Because most patients present weeks after the viral infection, antiviral therapy does not have a clear role in the treatment of myocarditis.[2] There is some evidence that interferon beta may be of some benefit.[30] The ESC has no specific recommendation regarding interferon beta therapy and recommends involvement of infectious disease in the decision.[23]

Intravenous Immunoglobulin (IVIG). The use of IVIG for the treatment of myocarditis is widespread, but its role is not clearly defined and there is conflicting evidence with regard to its benefit on survival and left ventricular function. Some studies have found high-dose IVIG may be of benefit in the treatment of acute myocarditis in the pediatric population with regard to left ventricular function and survival; others concluded that IVIG conferred no survival advantage or left ventricular normalization.[31,32,33] Even without clear evidence for its use, a significant number of patients with acute myocarditis receive IVIG, and some institutions include IVIG as a regular component of the management strategy for acute fulminant myocarditis (AFM).[3,8,22]

"IVIG is not recommended as a routine treatment for myocarditis" by the Canadian Cardiovascular Society."[20] The ESC provides no specific recommendation on the use of IVIG due to lack of multicenter randomized studies.[23]

Immunoadsorption. While not universally available, the use of

immunoadsorption in adult patients with inflammatory cardiomyopathy has been shown to improve left ventricular systolic function and decrease left ventricular end-diastolic diameter at 6 months.[34] The ESC gives no recommendation on the use of immunoadsorption due to lack of evidence.[23]

Immunosuppression. Immunosuppression in the treatment of myocarditis is, in general, controversial. However, immunosuppression for the treatment of specific entities, including giant cell and eosinophilic myocarditis, has been well established.[2,17]

Studies on immunosuppression for the treatment of myocarditis have included prednisone either alone or in combination with azathioprine or cyclosporine.[23,35] Favorable response has been seen primarily in virus-negative and giant cell myocarditis.[23]

A recent meta-analysis by Lu et al examined the role of immunosuppressive treatment for myocarditis in adults and children and included nine articles (609 patients; 342 treated with immunosuppression and 267 treated conventionally). The group receiving immunosuppressive treatments had improved left ventricular ejection fraction (LVEF) at short- and long-term follow-up and decreased left ventricular end diastolic diameter at short-term follow-up. There was no difference in mortality or need for transplantation. The authors concluded that while immunosuppressive therapy may be beneficial, more large randomized controlled trials (RCTs) are needed.[35]

A recent Cochrane systematic review by Chen et al looked more specifically at the use of corticosteroids for viral myocarditis and included eight RCTs and 719 participants. There was no significant difference in mortality between the steroid and control group. LVEF was improved in the short-term in the corticosteroid group. The authors concluded that corticosteroids do not reduce mortality, but they may improve cardiac function. They note, however, that this finding is questionable due to the size and quality of the trials and large-scale RCTs are needed.[36]

Even without compelling evidence to support the use of corticosteroids for the treatment of myocarditis in children, administration of steroids is not uncommon. Some studies show associated increased mortality or transplantation and no change in survival.[3,8]

Recommendations regarding the use of steroids for myocarditis have been set forth by the CCS, the Heart Failure Society of America (HFSA), as well as the ESC. Corticosteroids as a routine treatment for myocarditis are not recommended by the CCS or the HFSA.[20,27] The ESC has set forth more specific recommendations as shown in Table 8.[23]

Mechanical ventilation and circulatory support and transplantation. Assistance of the pediatric patient's respiratory system and mechanical circulatory support are commonly required in pediatric patients with myocarditis. Extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) have significant risks of complication, but can be life-saving and are often used as a bridge to transplantation or recovery. ECMO-associated complications include bleeding, limb ischemia, neurologic injury, multi-system organ failure, renal failure, sepsis, and circuit complications.[22] ECMO use in patients with acute fulminate myocarditis and hemodynamic collapse is the first-line mechanical circulatory support system due to ease and rapidity of set up, especially during CPR, when compared with VADs.[37]

The CCS recommends "for fulminant myocarditis, mechanical circulatory support should be considered. Invasive therapies are considered acceptable considering the prospect of spontaneous recovery."[20] The ESC recommendations state: "In patients with hemodynamic instability, a mechanical cardio-pulmonary assist device may be needed as a bridge to recovery or to heart transplantation" and "cardiac transplantation should be deferred in the acute phase, because recovery may occur, but can be considered for hemodynamically unstable myocarditis patients, including those with giant cell myocarditis, if optimal pharmacological support and mechanical assistance cannot stabilize the patient."[23]

Disposition. Due to the complicated nature of myocarditis and significant risk of clinical deterioration, patients often require admission to an intensive care unit or unit with capabilities to monitor patients for dysrhythmias and hemodynamic instability.[3,20] Additionally, hospitalization at a facility with the ability for cardiac catheterization and EMB should be considered.[23]

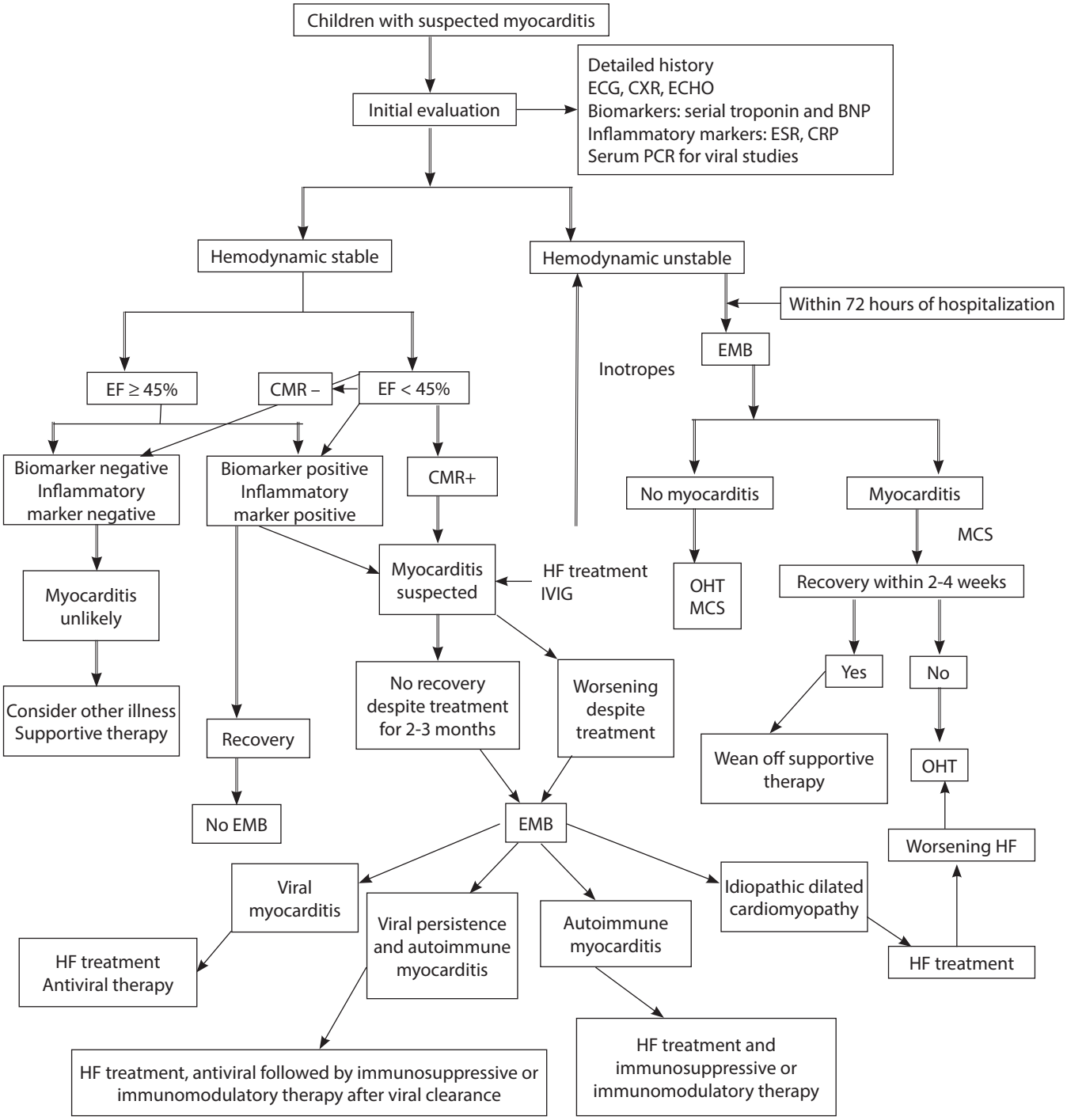
Additional Aspects

Misdiagnosis. Because of the varied presentation of myocarditis, the potential for misdiagnosis is high. Most commonly, myocarditis is misdiagnosed as a respiratory tract infection; sepsis and seizure are other common misdiagnoses.[4]

Outcome/Prognosis. Although there is potential for complete recovery from myocarditis, the diagnosis is associated with high rates of transplantation and mortality, especially in cases caused by parvovirus B19 and those that progress to fulminant myocarditis.[3,8,13,22] The overall mortality of pediatric myocarditis is 7.3%.[3] The rate of death or transplantation is higher for children younger than age 12 years as compared to older children.[3] Children with parvovirus B19 myocarditis have a worse prognosis. The rate of transplant-free survival for these children is only 32%.[13] In a study of 20 patients with acute fulminant myocarditis, the survival rate was 85%; one of the survivors in this study underwent transplantation.[22]

Sudden Death. Myocarditis can present as sudden death in childhood. Frequently diagnosed at autopsy, myocarditis is an etiology of sudden unexpected cardiac death and sudden unexpected death due to an infectious disease.[38,39] Myocarditis has also been identified as an etiology of sudden death in sports-related deaths.[40]

Figure 5. Algorithm for Diagnosis and Treatment of Suspected Pediatric Myocarditis[41]



Abbreviations: BNP = brain natriuretic peptide, CMR = cardiac magnetic resonance imaging, CRP = C-reactive protein, CXR = chest x-ray, ECG = electrocardiogram, ECHO = echocardiogram, EF = ejection fraction, EMB = endomyocardial biopsy, ESR = erythrocyte sedimentation rate, HF = heart failure, IVIG = intravenous immunoglobluin, MCS = mechanical circulatory support, OHT = orthotopic heart transplantation, PCR = polymerase chain reaction

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Follow-up. Patients with myocarditis may fully or partially recover. Relapses may occur. In those patients whose disease does not resolve, dilated cardiomyopathy may develop. Patients with myocarditis require long-term follow-up with clinical reassessment, ECGs, and repeat echocardiograms.[23] Patients with suspected myocarditis with mild symptoms should be followed closely as well due to potential for progression to severe illness.[20]

Summary

Myocarditis serves as a diagnostic challenge for the emergency physician in the pediatric population. Given the varied nature of presentation, the breadth of the clinical spectrum, and the limitations in treatment options, emergency physicians must keep a high index of suspicion for myocarditis. Figure 5 reviews the basics in diagnosis and treatment of myocarditis in children.[41]

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CME Questions

1. The most common etiology of myocarditis in the pediatric population is:
   a. bacterial.
   b. autoimmune.
   c. medication induced.
   d. viral.

2. A 2-year-old male patient presents to the ED for evaluation of cough, wheezing, and fever. Mother reports patient has not been eating well recently and has been more sleepy than normal. Nursing staff obtains the following vitals: heart rate 147, respiratory rate 34, pulse oximeter 91%, and temperature 38.9. Your initial assessment reveals a lethargic appearing male, minimally interactive during your exam, who is tachycardic and tachypneic. You hear a S3 gallop during auscultation, as well as wheezing throughout the lung fields posteriorly. Abdominal exam is unremarkable. You decide to try acetaminophen 15 mg/kg PO, an IV bolus of normal saline at 20 mL/kg, and an albuterol/atrovent nebulized breathing treatment, and see minimal response to treatment although the patient does start to defervesce. Which of the following plans would you do first?
   a. Discharge the patient home with follow up with 3-5 days.
   b. Discharge the patient home with follow up within 24 hours.
   c. Admit to the pediatric floor for continued resuscitation.
   d. Admit to the pediatric ICU for hemodynamic monitoring.

3. Initial treatment of a pediatric patient with suspected myocarditis in the emergency department includes:
   a. assessment of the patient's airway, breathing, and circulation and interventions to acutely stabilize the patient.
   b. obtain emergent for endomyocardial biopsy and cardiac catheterization.
   c. start inotropic support and prepare for intubation.
   d. obtain a chest CT.

4. Upon discharge, pediatric patients with myocarditis should:
   a. be instructed to refrain from any dairy products.
   b. limit physical activity for 6 weeks.
   c. limit physical activity for 6 months.
   d. call their primary physician to arrange follow up within 3 months.

5. Long-term management of pediatric patients with myocarditis includes:
   a. long-term therapy with antiviral agents.
   b. repeat electrocardiograms and echocardiograms to follow recovery.
   c. extended course of prednisone.
   d. referral for cardiac transplantation.

6. Pediatric myocarditis is most frequently seen in:
   a. white females.
   b. Hispanic males.
   c. white males.
   d. African American males.

7. For definitive diagnosis of myocarditis:
   a. cardiac biomarkers should be elevated.
   b. ECG findings should be consistent suggestive of cardiac injury.
   c. abnormal cardiac function should be seen on echocardiogram.
   d. histological or immunohistological evidence of myocarditis should be seen on endomyocardial biopsy.

8. Given the frequent etiology of viral causes of myocarditis, testing for the pathogen should:
   a. include antibody titers.
   b. include viral culture and isolation.
   c. include detection of viral genome.
   d. not be done routinely.

9. Which of the following regarding ICD and pacemaker therapy is true?
   a. Permanent pacemaker therapy should be initiated early in patients with acute viral myocarditis who present with second degree heart block.
   b. ICD implantation is indicated for patients with acute myocarditis who have symptomatic ventricular tachycardia.
   c. Early ICD implantation is indicated for severe, unstable left ventricular dysfunction in patients with viral myocarditis.
   d. Giant cell myocarditis has a better prognosis than infectious myocarditis and therefore early ICD or pacemaker implantation is contraindicated in these patients.

10. Prognosis for recovery from myocarditis is worst in which of the following patients?
    a. 10-year-old male with giant cell myocarditis requiring ECMO and ST segment changes on electrocardiogram
    b. 13-year-old female with viral myocarditis and symptomatic 2nd degree heart block
    c. 2-year-old male with echocardiogram findings suggestive of mild left ventricular end diastolic dysfunction
    d. 8-year-old female with moderately elevated CRP and ESR and hypotension responsive to fluid resuscitation

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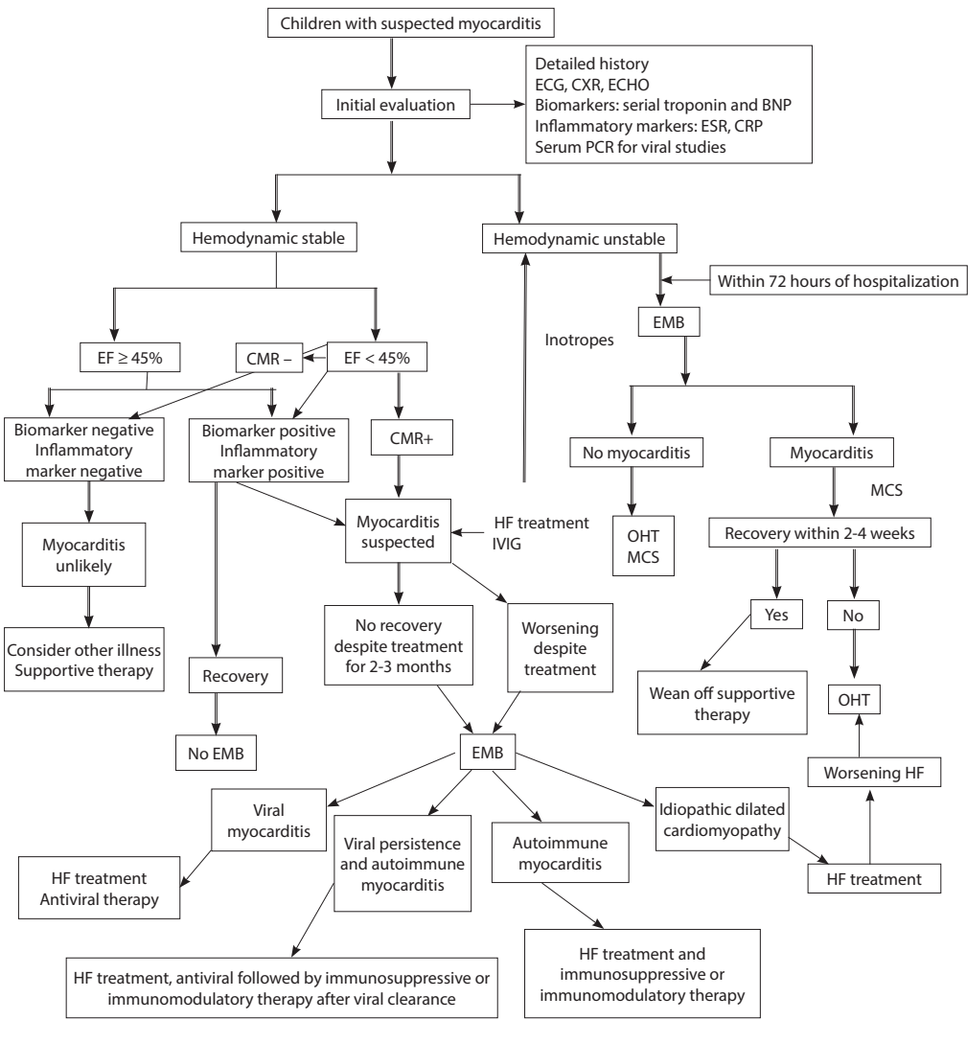
Practical, Evidence-Based Reviews in Pediatric Emergency Care

Pediatric Myocarditis

Algorithm for Diagnosis and Treatment of Suspected Pediatric Myocarditis[41]



Abbreviations: BNP = brain natriuretic peptide, CMR = cardiac magnetic resonance imaging, CRP = C-reactive protein, CXR = chest x-ray, ECG = electrocardiogram, ECHO = echocardiogram, EF = ejection fraction, EMB = endomyocardial biopsy, ESR = erythrocyte sedimentation rate, HF = heart failure, IVIG = intravenous immunoglobluin, MCS = mechanical circulatory support, OHT = orthotopic heart transplantation, PCR = polymerase chain reaction

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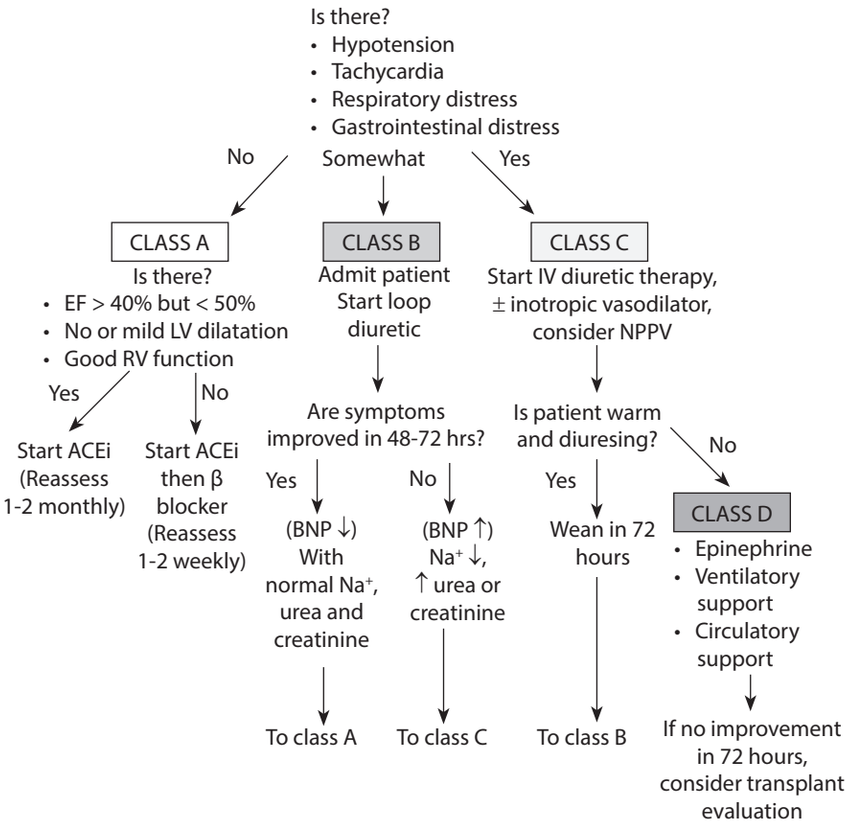
Diagnostic Criteria for Myocarditis[19]

Criteria		Histological Confirmation	Biomarker, ECG, or Imaging Abnormalities Consistent with Myocarditis
Possible subclinical acute myocarditis	In the clinical context of possible myocardial injury without cardiovascular symptoms and one or more 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	Absent	Required
Probable acute myocarditis	In the clinical context of possible myocardial injury with cardiovascular symptoms and one or more 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	Absent	Required
Definite myocarditis	Histological or immunohistological evidence of myocarditis	Required	Not Required

ECG = electrocardiogram

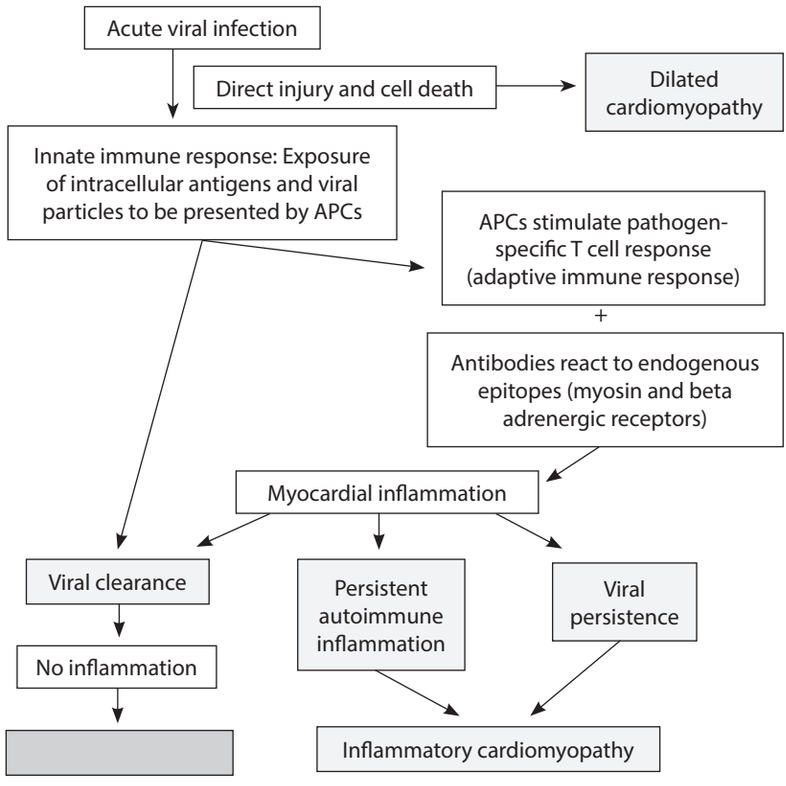
Adapted from: Sagar S, Liu PP, Cooper LT Jr. Myocarditis. *Lancet* 2012;379:738-747.

Algorithm for Heart Failure Management[20]



Reprinted with permission from: Kantor PF, Lougheed J, Dancea A, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Can J Cardiol* 2013;29:1535-1552.

Pathogenesis of Myocarditis[17]



Reprinted from: Shauer A, Gotsman I, Keren A, et al. Acute viral myocarditis: Current concepts in diagnosis and treatment. *Isr Med Assoc J* 2013;15:180-185.

Supplement to *Pediatric Emergency Medicine Reports*, November 2014: "Pediatric Myocarditis." Authors: Heather A. Heaton, MD, Instructor of Emergency Medicine, Department of Emergency Medicine, Mayo Clinic, Rochester, MN; and Virginia Keaveny, MD, Emergency Medicine Resident, Mayo Clinic, Rochester, MN.