Evaluation And Management Of Pediatric Acute Infectious Myocarditis

During a rare slow evening shift, the triage nurse notifies you that he has just put a sick infant into the resuscitation bay. The parents of the 2-month-old baby boy brought him to the emergency department because he “didn’t look right.” His father reports that for the past 24 hours, his son has been fussy and felt hot to the touch. The family initially attributed the boy’s condition to the recent hot weather, especially because their air conditioner is broken. However, for the past 8 hours, the boy has refused formula, and has started “breathing funny.”

As you enter the room, the nurse reports that the patient has a rectal temperature of 38.5°C (101.3°F), that he is unable to obtain a cuff blood pressure, and that the pulse oximeter will not pick-up. You look up at the cardiac monitor to see a heart rate of 205 bpm. The infant is listless and grunting. His extremities are mottled and cold with weakly palpable pulses. Cardiac auscultation is confounded by the baby’s grunting and tachycardia, but there seems to be a systolic murmur. His liver edge is palpable below his umbilicus. What is the etiology of this infant’s shock state? Is he septic? Does he have a dural dependent congenital heart lesion? Is he septic? Does he have a ductal dependent congenital heart lesion? Is the baby hypovolemic? Is the baby hypoxic? Is the baby hypothermic? Is the baby hypoglycemic? Is the baby hypocalcemic? Is the baby hypokalemic? Is the baby hypomagnesemic? Does he have a congenital heart defect? Does he need to be intubated? What drugs should you use for the intubation?

You make the decision to intubate him. With judicious use of fentanyl and rocuronium, and with the code cart open and nearby, you successfully intubate him. Despite his poor perfusion, one of the nurses can get enough blood for an arterial blood gas and lactate level which reveal a pH of 7.0, PaCO2-50, PaO2-60, and a base deficit of -20, with a lactate level of 15 mmol/L. You alert the on-call cardiologist and the cardiac intensive care team. You make the decision to start a prostaglandin infusion? … an inotropic infusion? Does he need to be supported with a hemodynamic monitor? Does he need to be transferred to the intensive care unit for further management? Does he need to be transferred to the pediatric intensive care unit for further management? Does he need to be transferred to the cardiac intensive care unit for further management? Does he need to be transferred to the surgical intensive care unit for further management?

Method of participation: Print or online answer form and evaluation

Prior to beginning this activity, see “Physician CME Information” on back page.

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CME Objectives

Upon completing this article, you should be able to:
1. Diagnose the signs and symptoms of acute myocarditis.
2. Delineate the possible ancillary testing available in support of the diagnosis.
3. Describe the complicating factors involved in making a definitive diagnosis of acute myocarditis.
4. Describe the initial management of a patient with acute, uncompensated heart failure.

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care service, and suggest that they mobilize the Extracorporeal Life Support (ECLS) team. The patient’s chest radiograph demonstrates cardiomegaly and pulmonary edema. The electrocardiogram (ECG) demonstrates sinus tachycardia. The echocardiogram demonstrates severe globally depressed biventricular function with moderate mitral regurgitation. Should the patient be placed on extracorporeal membranous oxygenation (ECMO) immediately? Which inotropic infusion should you start in the mean time? ... dopamine? ... dobutamine? ... milrinone? You decide to start him on a dobutamine infusion.

A
cute myocarditis has a wide spectrum of presentation: from mild flu-like symptoms, to acute cardiovascular collapse. Commonly, the disease course is progressive. Therefore, the ED physician should have a high index of suspicion for the disease when caring for infants and children with viral symptomatology, especially when their intuition tells them, “Something is not quite right with the patient.” While much of the management of the disease is supportive, early and accurate diagnosis and treatment are paramount for a favorable outcome. In this issue of Pediatric Emergency Medicine Practice, we will review an evidence-based approach to the evaluation and treatment of children with acute infectious myocarditis.

Abbreviations Used In This Article

BNP: B-type Natriuretic Peptide
CE-MRI: Contrast Enhanced Magnetic Resonance Imaging
EBV: Epstein-Barr virus
ECG: Electrocardiogram
ECLS: Extracorporeal Life Support
ECMO: Extracorporeal Membranous Oxygenation
ECPR: Extracorporeal Cardiopulmonary Resuscitation
EMS: Emergency Medical Service
HFSA: Heart Failure Society Of America
HIV: Human Immunodeficiency Virus
HLA: Human Leukocyte Antigen
HSV: Herpes Symplex Virus
LV: Left Ventricular
LVEF: Left Ventricular Ejection Fraction
P2C2 HIV: Pediatric And Cardiac Complications Of Vertically Transmitted HIV Infection
PALS: Pediatric Advanced Life Support
PCR: Polymerase Chain Reaction
RNA: Ribonucleic Acid
RSV: Respiratory Syncytial Virus

Critical Appraisal Of The Literature

The majority of the current literature on pediatric myocarditis consists of review articles, case reports, and retrospective studies. The scarcity of prospective research in the pediatric population is explained by the difficulty of enrolling an adequate number of patients as well as the current disagreement on what actually constitutes the diagnosis of myocarditis.

Appraisal Of Current Literature: Clinical Presentation

There is significant overlap between the primary signs and symptoms of myocarditis and other common childhood illnesses. The axiom “tachycardia out of proportion to the fever” is often quoted as a clinical “red flag” for myocarditis. However, this sign has minimal utility in an anxious child in the emergency department setting. Data on the clinical presentation of myocarditis in pediatrics patients come from retrospective reviews of presumed cases; therefore, they suffer from inaccuracies of documentation at the time of the original presentation. In a retrospective review of 41 adult patients with histologically-proven myocarditis, Pinamonti reported that the presenting signs and symptoms included congestive heart failure in 63%, atrioventricular block in 17%, chest pain in 15%, and supraventricular arrhythmias in 5%. While determining the frequency of specific signs and symptoms is not possible, it is expected that a significant percentage of patients will present with decompensated heart failure. Clinical guidelines exist for the general evaluation of patients with acute decompensated heart failure. These guidelines were developed by a panel of experts and published by the Heart Failure Society Of America (HFSA).

Appraisal Of Current Literature: Diagnosis

Despite its well-established morbidity and mortality, there are no published guidelines for the clinical diagnosis of myocarditis. Considerable debate remains about the criteria necessary to make a definitive diagnosis of myocarditis. The Dallas criteria were proposed by Aretz et al in 1986 to define and classify myocarditis based on the histopathology of endomyocardial specimens. The diagnosis of myocarditis requires an inflammatory infiltrate with associated myocyte necrosis. If there is a mild inflammatory infiltrate without light microscopic
evidence of myocyte destruction, the specimen is considered borderline. Recently, the universal use of the Dallas criteria has been challenged due to their limited sensitivity and specificity and the invasiveness needed to obtain an appropriate specimen.\(^6\) Considering these issues, making a reliable diagnosis of myocarditis remains a significant challenge.

Chest radiography and electrocardiography are frequently used when making management decisions in patients with suspected myocarditis. Although cardiomegaly and pleural effusions may be evident on chest radiography, they are not specific for myocarditis. The electrocardiogram (Figure 1) often shows the non-specific finding of sinus tachycardia with low voltage QRS complexes (total QRS amplitude less than 5 mm in all precordial leads). Inflammation of the conduction system leads to a wide range of dysrhythmias. Retrospective reviews report the occurrence of atrial arrhythmias, complete heart block and ventricular arrhythmias in patients with myocarditis.\(^7\)\(^{11}\) In addition, electrocardiographic findings in patients with myocarditis may also be similar to those of patients with acute myocardial infarction.\(^12\)\(^{13}\) However, given the unlikelihood of coronary artery disease in pediatric aged patients, myocarditis should be considered when these ECG findings are present.\(^13\)

Historically, the diagnosis of viral myocarditis has been based on the identification of virus by either peripheral culture or serial serology. Viral cultures of peripheral specimens such as blood, stool, or urine are commonly performed but are unreliable. Viral serology is non-specific and time consuming since it requires serial analysis. There is an increasing volume of literature demonstrating the use of real-time PCR in the identification of microbial pathogens in blood or infected tissue. As an added benefit, real-time PCR also provides a tool for providing quantitative results of target viral nucleic acid present in a clinical sample. The utility of PCR for the diagnosis of myocarditis was assessed in a study by Martin.\(^14\) PCR was used to analyze 38 myocardial tissue samples from 34 patients with suspected acute viral myocarditis and 17 control patients with congenital heart disease or hypertrophic cardiomyopathy. Using PCR primers, myocardial samples were evaluated for the presence of enterovirus, cytomegalovirus, adenovirus, and herpes simplex virus. In some cases, blood samples were drawn for serologic evaluation and/or culture at the time of cardiac catheterization. In 26 of the 38 (68%) myocardial samples from myocarditis patients, viral genome was detected by PCR, whereas all control samples were negative. Serology, when obtained, (n=12) were not considered positive in any of the patients (i.e., no acute titers were significantly elevated, and paired titers did not reach fourfold elevation). Nine peripheral cultures from various sites were positive for virus, and when compared to PCR viral identification in the same individual, there was 100% agreement. Eleven of 13 patients undergoing endomyocardial biopsy and 1 of 4 patients undergoing cardiac transplantation had concomitant blood samples analyzed by PCR. None of these blood samples amplified viral genome, even though some of these patients’ tissue specimens amplified viral genomes by PCR evaluation. The authors postulated that the blood samples were uniformly negative because of the possibility of rapid clearance of virus from the bloodstream, lower viral content in blood versus solid tissue, or problems in the handling of blood samples since some of the samples had been stored for years prior to undergoing PCR evaluation.\(^14\)

A study by Akhtar et al evaluated the utility of PCR analysis in identifying the viral genome in tracheal aspirates of intubated children.\(^15\) Tracheal aspirate samples were obtained from 32 intubated patients with childhood viral pneumonia. Seven of the 32 patients were diagnosed with myocarditis by endomyocardial biopsy. Although the number of subjects with both tracheal aspirates and endomyocardial biopsy samples was small, the sensitivity of tracheal aspirate for predicting the PCR results on biopsy was 100%.

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**Figure 1. Electrocardiogram Showing Sinus Tachycardia With Low Voltage QRS In A Patient With Myocarditis**

![Image reprinted with permission from Dr. Salerno](image-url)
Serum creatine kinase (CK-MB), and troponin I and T are routinely measured when myocarditis is suspected. Smith et al measured troponin I in a subgroup of 88 patients that had been enrolled in the Multicenter Myocarditis Treatment Trial. Troponin was elevated in 18 of 53 patients with biopsy proven myocarditis and in 0 of 35 patients with unexplained heart failure and no biopsy evidence of myocarditis. The sensitivity of an elevated troponin for the diagnosis of myocarditis was 0.34, the specificity was 0.89, and the positive predictive value was 82%. The authors concluded that an elevated troponin in a patient with unexplained heart failure, should suggest the possibility of myocarditis. This same study showed that there were no significant differences in CK-MB values between those with myocarditis and those without (p=.27) suggesting that CK-MB is not a useful general screening tool for myocarditis.

Non-invasive myocardial imaging techniques for the diagnosis of myocarditis include echocardiography, nuclear imaging with gallium, and nuclear magnetic resonance imaging. Echocardiography is currently recommended as the initial diagnostic study for all patients with suspected myocarditis. Several adult studies have addressed the role of echocardiography in the diagnosis of myocarditis. Pinamonti et al retrospectively analyzed echocardiographic findings among 41 patients with biopsy proven myocarditis. Though left ventricular dysfunction occurred in 69%, significant left ventricular cavity enlargement was uncommon. Because these findings are similar to those from other forms of acute dilated cardiomyopathy, they are nonspecific for the diagnosis of myocarditis. Contrast enhanced magnetic resonance imaging (CE-MRI) appears to be the most promising non invasive imaging technique for identifying myocardial inflammation and myocyte injury in patients with presumed myocarditis. Friedrich et al used cardiac MRI to assess 44 patients with symptoms of acute myocarditis and compared the findings to 18 control patients. With serial evaluation by CE-MRI during the first 2 weeks of illness, they were able to localize and determine the extent of inflammation in the study patients.

A number of clinical trials, also non-specific for myocarditis, have tried to assess the utility of B-type natriuretic peptide (BNP) in the diagnosis of acute heart failure. Elevated plasma BNP concentration correlates with increased cardiac filling pressures and ventricular dysfunction. Guidelines from the HFSA for the evaluation of acute decompensated heart failure include the measurement of BNP. Although it is still probably considered the gold standard, endomyocardial biopsy is reserved for patients who have an acute deterioration of cardiac function of unknown etiology and who are unresponsive to medical therapy (HFSA Class Of Evidence = C). The recommendation is based on distinct clinical forms in which endomyocardial biopsy establishes the diagnosis and treatment options. These include fulminant myocarditis, giant cell myocarditis, and eosinophilic myocarditis.

**Appraisal Of Current Literature: Treatment**

The routine use of immunosuppressive therapy for patients with myocarditis is not recommended. This recommendation exists as part of published treatment guidelines from the HFSA and is based on expert consensus opinion. There have been randomized controlled studies designed to examine the utility of immunosuppressive agents for treatment of myocarditis. The Parillo study randomly assigned 102 patients with dilated cardiomyopathy to treatment with prednisone (60 mg/day) or placebo for 3 months. The authors concluded that prednisone had only marginal clinical benefit and should not be administered as standard therapy. The study has received criticism due to a small number of biopsy-proven cases of myocarditis in the study population. The Myocarditis Treatment Trial evaluated immunosuppressive therapy with prednisone and cyclosporine in patients with histologically verified myocarditis and a left ventricular ejection fraction (LVEF) less than 45%. The study subjects were randomized to receive conventional therapy alone or combined with immunosuppression for 6 months. For the entire group, the LVEF improved from 25% at baseline to 34% at 28 weeks. However, the mean change in LVEF did not differ between groups. There was also no difference in survival between groups. The authors concluded that routine use of immunosuppressive therapy produced no clinical benefit.

Routine use of immunoglobulin is also not recommended for patients with myocarditis. Guidelines exist from the HFSA that state that intravenous immunoglobulin (IVIG) therapy does not provide benefit to patients with new onset cardiomyopathy and myocarditis. There is a single prospective randomized multicenter trial evaluating the use of immunoglobulin in patients with cardiomyopathy...
of less than 6 months duration and symptomatic heart failure. All patients underwent endomyocardial biopsy. Only 16% of the 62 randomized patients met the Dallas histopathologic criteria for myocarditis. Follow-up at 6 and 12 months showed equivalent improvement in left ventricular ejection fraction, survival, and functional capacity between the 2 groups. A Cochrane analysis also concluded that there was no convincing evidence supporting the use of IVIG for the treatment of presumed viral myocarditis. This conclusion was largely based on a paucity of well-designed studies. The author did note that there were multiple case reports and case series reporting dramatic responses to IVIG in adults and children with acute myocarditis.

Antiviral Therapy
There are no randomized clinical trials directly assessing the efficacy of antiviral therapy in the treatment of myocarditis. There are several case reports commenting on the benefits of ganciclovir therapy in viral associated myocarditis. There are also several clinical trials using interferon beta that have demonstrated beneficial effects. Interferon beta is derived from fibroblasts and plays an important role in the natural defense against viruses. In a study by Kuhl et al, 22 adult patients with biopsy proven persistent viral cardiomyopathy were treated with recombinant beta interferon. During treatment, there was evidence of viral clearance that was associated with decreased myocardial inflammation and an improvement in ventricular function and heart failure symptoms in 67% of the patients. Finally, attenuated vaccines have been used to prevent the development of myocarditis after viral challenge in animals. However, the usefulness of vaccines in humans remains unclear.

Epidemiology And Etiology
Myocarditis is an insidious disease that often presents with generalized signs and symptoms consistent with a common “flu-like” illness. Likely, a portion of cases of myocarditis lack cardiac-specific symptoms, and resolve without identification. Further complicating epidemiologic assessment are patients on the other end of the spectrum who suffer sudden death, some of whom escape detection due to incomplete post-mortem examination. This uncertainty is compounded by the disagreement about the histopathologic criteria for diagnosis and the inability to isolate a causative pathogen in even clinically apparent cases. Therefore, though the overall, all-cause incidence of the disease is indeterminate, data estimating the incidence in specific studied populations is reported below.

Although there are several known infectious causes of myocarditis (Table 1), in patients without a preexisting medical condition, acute myocarditis most commonly has a viral etiology. Traditionally, the diagnosis of viral myocarditis has been made by isolation of virus from peripheral tissue/blood culture or by antibody serology in a patient with suggestive signs and symptoms. Recently, PCR has been used to isolate viral sequences from tissue samples from patients presumed to have myocarditis. Because variables such as patient age, geography, and seasonal variation affect the epidemiology of viral infection, no conclusions regarding the relative frequency of particular viruses can be made from reports. Most authors conclude that the family of enteroviruses and adenovirus are the 2 most common viral causes of myocarditis. However, a recent study also implicates parvovirus 19 and human herpesvirus-6 as common pathogens. In the largest report to date, Bowles et al aimed to define the common etiologies of viral myocarditis. They used the PCR technique to examine specimens from 773 patients of all ages with the clinical diagnosis of either myocarditis (n=624) or dilated cardiomyopathy (n=149). Of the 624 patients with myocarditis, PCR amplified viral genome from endomyocardial specimens in 239 (38%). One-hundred-forty-two (23%) were positive for adenovirus, 85 (14%) were positive for entero-viruses, 18 (3%) were

Table 1. Infectious Causes Of Myocarditis

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Viral</td>
<td>Coxsackievirus, adenovirus, HIV, CMV, Parvovirus, EBV, hepatitis C, HSV, influenza A and B, echovirus, RSV, measles, rubella, rabies</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Corynebacterium diphtheriae, H. flu, Gonococcus, mycoplasma pneumoniae, Mycobacterium, Salmonella, Staph. aureus, Strep. pyogenes, Treponema pallidum</td>
</tr>
<tr>
<td>Fungal</td>
<td>Actinomycetes, aspergillus, candida, coccidioides, blastomyces, cryptococcus, histoplasma, mucormycoses, nocardia</td>
</tr>
<tr>
<td>Protozoal</td>
<td>Trypanosoma cruzi (Chagas disease), Toxoplasma gondii</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Ascaris, Schistosoma, Trichinella spiralis</td>
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positive for cytomegalovirus, and less than 1% of the patients were positive for parvovirus, influenza A, herpes simplex virus 5 (HSV 5), Epstein-Barr virus 3 (EBV 3), or Respiratory Syncytial virus 1 (RSV 1).

Important epidemiologic and etiologic data also come from post-mortem examination of cases of sudden death. In case series evaluating the causes of sudden death, myocarditis is reported as a cause in between 5% and 35%.40-46 Again, the true incidence of myocarditis among patients who suffer sudden death is indeterminate due to the subset of such patients that do not undergo a thorough post-mortem examination. Because most of the published series of individuals who suffer sudden death from myocarditis do not evaluate for an etiologic infectious agent, there can be no definitive correlation between disease severity/risk for sudden death and a particular virus. However, Bowles et al found less extensive histopathologic evidence of myocardial inflammation in those with adenovirus as compared to those with enterovirus myocarditis.36

Pathophysiology

The pathophysiology of viral myocarditis is complex and not completely understood. However, there have been several recent review articles that summarize the current state of knowledge of the pathobiology.47-54 In their review article, Liu and Mason suggest that the disease consists of three different and successive phases: viral infection, autoimmunity, and dilated cardiomyopathy.52 They suggest that each of the phases is distinct, but that they “...evolve into the other with transitional periods of indistinctness.” In the initial phase, the infecting virus enters the myocyte. In the case of coxsackievirus and adenoviruses this occurs via the coxsackie-adenovirus receptor on the myocyte surface. Viral entry and replication trigger an immune response directed toward the infected cells. This marks the transition to the second or “autoimmunity” phase. The ultimate goal of the immune response is to identify and destroy infected cells, effectively ridding the body of virus. However, it is thought that in some individuals, an over-exuberant inflammatory response is triggered. This leads to excessive destruction of myocytes, thus decreasing the number of contractile elements. This negatively impacts the underlying myocardial architecture, resulting in worsened cardiac function.

In addition to data supporting the autoimmune-

Differential Diagnosis

Because the cardiac manifestations of nonfulminant myocarditis frequently remain subclinical or present as part of a generalized flu-like illness, the differential diagnosis is quite broad, and encompasses most conditions that present with constitutional symptomatology. Everyday realities of emergency medicine practice, such as high patient volumes and limitations on observation time, make it difficult to differentiate between a patient who has a routine viral illness and one who is in the initial stages of a progressive case of myocarditis. This is especially true in pediatric emergency practice given the high percentage of patients with uncomplicated viral illness. Table 2 illustrates clinical findings that suggest myocarditis.

Despite the complexities of assessing subtle cases of myocarditis, recognition and management of fulminant cases are the emergency medicine practitioner’s greater challenges. Perhaps the most vexing scenario for the ED physician is a patient who presents with the combination of acute heart failure and dysrhythmia. Determining which is the primary process can be a difficult task, but this distinction is vital because treatment and expected clinical course differ

<table>
<thead>
<tr>
<th>Table 2. Clinical Findings Suggesting Myocarditis</th>
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<tbody>
<tr>
<td>• Flu-like illness in the preceding month</td>
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<tr>
<td>• Symptoms of fatigue, malaise, shortness of breath, and chest pain</td>
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<tr>
<td>• Evidence of congestive heart failure on physical examination</td>
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<tr>
<td>• Elevated troponin level</td>
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<tr>
<td>• Atrioventricular block or arrhythmia on electrocardiography</td>
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<td>• Decreased ventricular function by echocardiography</td>
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Prehospital Care

The majority of patients with a febrile illness, including those with myocarditis, will be brought to the emergency department by their caregivers rather than being transported by emergency medical service (EMS) personnel. Early and aggressive fluid resuscitation is the hallmark of therapy for many etiologies of shock. As such, administration of crystalloid solutions is a common first “knee-jerk” response when EMS responders are faced with a critically ill patient. However, the group of patients with acute myocarditis and resultant cardiogenic shock is a prime example of why this practice cannot be condoned. On occasion, a patient suffers cardiovascular collapse with resultant cardiac arrest or has a life-threatening arrhythmia. In such cases, prehospital care includes emergency stabilization per Pediatric Advanced Life Support (PALS) Guidelines and rapid transport to an emergency department, preferably one in an institution that can offer ECLS on an emergent basis. Although this capability is currently relatively uncommon, there are emerging data that support the use of rapid deployment extracorporeal life support, so-called extracorporeal cardiopulmonary resuscitation (ECPR), in cases of cardiac arrest with ongoing cardiopulmonary resuscitation (CPR). Though the percentage of good outcomes from these cases remains modest at best, the results are more encouraging when one considers that most, if not all, of these patients would have died if such measures had not been undertaken.

Prehospital care of the child with potential myocarditis:
- Cardiac monitoring
- Pulse oximetry
- Supplemental oxygen
- Assisted ventilation
- Venous access
- Judicious use of intravenous fluid
- Inotropic support and management of low cardiac output
- Electrical cardioversion and defibrillation
- Assess for hypoglycemia

ED Evaluation

History

The clinical presentation of myocarditis is variable and is based on a variety of factors including the degree of myocardial involvement, patient age, and immunologic status. In its most fulminant form, myocarditis is characterized by rapid progression to cardiovascular collapse. This occurs in approximately 10% of known cases. In contrast to fulminant myocarditis, many cases of myocarditis likely go unrecognized because the cardiovascular symptoms are vague and overlap with other common pediatric diagnoses. Myocarditis should be considered in patients with tachycardia and respiratory distress, particularly those with hemodynamic compromise or arrhythmias.

Infants with myocarditis may present with irritability, pallid spells, listlessness, poor feeding, and diaphoresis. These symptoms may precede the sudden onset of cardiovascular collapse. Beyond the infant age group, initial symptoms may include lethargy, low-grade fever, myalgia, arthralgia, and malaise. Young children may complain of abdominal pain and decreased appetite. Older children often complain of chest pain of similar nature to the pain associated with myocardial infarction. In addition, caregivers frequently give a history of a recent flu-like illness 10 to 14 days prior to presentation. However, the presence of a viral prodrome is highly variable, ranging from 10% to 80% of patients with documented myocarditis. If congestive heart failure has developed, diaphoresis, palpitations, orthopnea, shortness of breath, and dyspnea on exertion may occur. Syncope or sudden death may also occur.

Because of this wide spectrum of presenting signs and symptoms, EM physicians must maintain a high index of suspicion for the disease. At a minimum, the diagnosis of myocarditis should be considered in all pediatric patients with new onset congestive heart failure in whom no other etiology is found.

Physical Examination

The initial evaluation of a patient presenting with myocarditis should include a thorough assessment of their hemodynamic status. Tachycardia, poor perfusion, altered mental status, and respiratory distress are ominous signs of hemodynamic collapse and the need for immediate intervention. The physical examination findings are those of a patient with congestive heart failure, including jugular venous distention, tachycardia, a gallop rhythm, and hepatomegaly. The precordium may be hyperdynamic. Left ventricular dilation may affect mitral valve leaflet coaptation, resulting in mitral regurgitation. Therefore, a harsh, holosystolic murmur is often heard at the apex. The
intensity of the murmur generally reflects the degree of mitral regurgitation. In the presence of a large pericardial effusion, the heart sounds are muffled. Pallor, mild cyanosis, cool extremities, and mottling are frequently present due to the compensatory systemic vasoconstriction from low cardiac output. A varying degree of respiratory distress may be evident with grunting and tachypnea. Pulmonary auscultation may reveal fine crackles in the lung bases consistent with pulmonary edema.

**Diagnostic Studies**

**Serum Studies**

Standard laboratory tests include: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, liver function tests, and urinalysis. It is recommended that BNP be assessed in all patients suspected of having heart failure when the diagnosis is not certain. A troponin level should be obtained when myocarditis is suspected, particularly in the patient presenting with chest pain. Serum PCR can be useful in identifying the viral pathogen, particularly in infants.

**Imaging Studies**

While echocardiography is the imaging study of choice when myocarditis is suspected, it generally requires the presence of a cardiologist. A chest radiograph and electrocardiogram are more readily available in the typical ED, and, therefore, serve as good initial screening tools. The chest radiograph frequently demonstrates cardiomegaly with pulmonary edema and pleural effusion. The ECG should guide decisions regarding the need for antiarrhythmic medications or the need for a temporary pacing device. Decisions regarding the use of inotropes, vasodilators, and diuretics can be directed by the echocardiographic findings (such as atrial and ventricular dilation, pericardial effusion, and ventricular dysfunction). Other imaging modalities (such as cardiac MRI and nuclear imaging) may be helpful for diagnostic purposes but are generally not applicable to the EM physician.

**Viral Studies**

Viral diagnosis has been historically based on identification of virus by peripheral culture or serial serology. These studies remain helpful as supportive diagnostic data. Specimens from the blood, nasopharynx, and rectum should be sent for culture and PCR of common viruses. In addition, specimens from other sources such as the urine or trachea may be obtained if clinically indicated.

**Treatment**

Initial ED management includes respiratory and circulatory stabilization, with appropriate transfer plans as necessary. It is important to consider cardiology consultation early in the management of the patient with myocarditis as these patients can deteriorate rapidly. Frequent assessment of vitals signs and continuous saturation monitoring is indicated. Endotracheal intubation may be required if the child has significant respiratory distress or evidence of cardiovascular collapse. Intravenous access is a necessity and should be obtained early in the evaluation.3

Arrhythmia management includes the use of pharmacologic therapy or cardioversion as appropriate for tachyarrhythmias.4 In the case of atrioventricular block with a bradycardic escape rhythm, transtheal or transvenous pacing may be required. For more information, please see the June 2006 issue of Pediatric Emergency Medicine Practice: The Evaluation and Management of Pediatric Cardiac Tachyarrhythmias: An Evidence-Based Approach.

For patients presenting in congestive heart failure, management should be directed by the HFSA guidelines.5 A summary of the recommendations are as follows: (See back page for strength of evidence definitions)

- Patients with congestive heart failure and evidence of fluid overload should be treated initially with intravenous loop diuretics. (Strength of Evidence = B)
- Intravenous vasodilators (intravenous nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. (Strength of Evidence = C)
- Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced heart failure characterized by left ventricular (LV) dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome) (Strength of Evidence = C).

(continued on page 10)
Clinical Pathway: Assessment And Management Of Pediatric Acute Myocarditis

Systemic illness consistent with myocarditis (tachycardia, shortness of breath)

YES

Cardiovascular compromise?

YES

Pediatric Advanced Life Support Guidelines

NO

Diagnostic studies
Electrocardiogram
Chest x-ray

NORMAL

ABNORMAL

History consistent with myocarditis (preceding flu-like illness, fatigue, malaise, dyspnea, chest pain, palpitations)

NO

Consider Additional Studies
Echocardiogram
Troponin level
BNP level

YES

ABNORMAL

Treatment
Heart failure management
Arrhythmia management
Consider intravenous immunoglobulin

Consider alternative diagnosis

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Administration of intravenous inotropes (milrinone or dobutamine) in the setting of acute decompensated heart failure should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C)

If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)

The routine use of invasive hemodynamic monitoring in patients with acute decompensated heart failure is not recommended. (Strength of Evidence = A) Ventricular assist devices have been utilized in patients who are refractory to conventional therapy.

Standard laboratory tests include: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B) It is recommended that BNP be assessed in all patients suspected of having heart failure when the diagnosis is not certain. (Strength of evidence = B)

Additional tests include an electrocardiogram to assess cardiac rhythm and conduction (Strength of Evidence = B) and a posteroanterior and lateral chest x-ray examination for determination of heart size, evidence of fluid overload, and detection of pulmonary, and other diseases. (Strength of Evidence = B)

Special Circumstances

Immunoincompetent patients

There are several case reports describing unusual, opportunistic infections of the myocardium in immunoincompetent patients. Human Immunodeficiency Virus (HIV) infected children represent an important subset of such patients that is at high risk for myocarditis. In 1999, the Pediatric and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group reported an incidence of 10.7% (younger cohort) and 15.3% (older cohort) among 2 groups of patients. However, this report was not designed to determine a specific etiology of ventricular dysfunction in these HIV infected children. In the paper, the group speculated that the cause of ventricular dysfunction in HIV infected children is likely to be multifactorial, and they included myocarditis as one possibility. In support of this are reports from other groups demonstrating the presence of HIV virus genomes in the myocardium of infected patients. In a follow up report in 2002, the P2C2 HIV Study Group reported a 5 year incidence of ventricular dysfunction of 17.7% and 39.1% respectively for the 2 cohorts. Therefore, myocarditis is a concern in the setting of HIV infection.

Risk Management Pitfalls For Pediatric Acute Myocarditis

1. Failure to identify myocarditis in a patient presenting with respiratory distress and cardiomegaly on chest radiograph.

2. Failure to identify myocarditis in a patient presenting with new onset recalcitrant arrhythmias.

3. Failure to have resuscitative equipment available.

4. Failure to recommend emergency department evaluation when a parent calls to say their child just recovered from a febrile illness one week ago and now is breathing funny.

5. Failure to distinguish signs of congestive heart failure from other systemic viral illnesses.

6. Failure to arrange transfer to an institution with ventricular assist devices.
tis should be considered in HIV infected children who present with suggestive signs and symptoms of heart failure.

**Connective Tissue Disorders**

Patients with connective tissue disorders may develop myocarditis as part of their clinical syndrome. The myocardial inflammation in this form of myocarditis is thought to be autoantibody mediated. While the initial evaluation and management of these patients should follow general heart failure guidelines, patients with connective tissue disorders and myocarditis are probably more likely to respond to immunosuppressive agents than those with infectious myocarditis. As with infectious myocarditis, the true incidence of myocarditis in patients with connective tissue disorders is unknown. However, based on review of case series, it is thought to be uncommon in adults and even less so in children.

**Chagas Disease**

Although not a common etiology of myocarditis in North America, Chagas disease should be considered in patients who present with heart failure and a history of travel to endemic areas in Central and South America. Caused by the protozoan parasite *Trypanosoma cruzi*, the disease has acute and chronic phases. Children more commonly present in the acute phase than adults do. When present, cardiac manifestations include atrial and ventricular arrhythmias and ventricular dysfunction. The disease is not cured spontaneously. Rather, antimicrobial treatment involves benznidazole or nifurtimox and supportive therapy for heart failure symptoms.

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**Controversies And Cutting Edge**

**Controversies**

Interestingly, the Dallas Criteria, which were introduced in 1986 to minimize the disagreement in the diagnosis, have now become the center of the controversy. Using endomyocardial biopsy specimens, the Dallas Criteria provided a histopathologic definition of myocarditis. However, endomyocardial biopsy sampling error, variation in the interpretation of the biopsy sample, and variance with viral PCR studies and immune activation markers are reasons why the Dallas criteria are no longer considered adequate to identify patients with viral myocarditis. A new consensus definition of viral and post viral immune related myocarditis is required to allow identification of different subsets of patients that may be responsive to specific treatment regimens.

The routine use of immunoglobulin for patients with myocarditis remains controversial. The authors of the Heart Failure Practice Guidelines were cognizant of the fact that the ability to detect markers of immune upregulation and anticardiac antibodies may soon allow identification of patients who might respond well to immunosuppressive regimens. They concluded that currently there is insufficient data to recommend the universal use of immunosuppressive medications, but provided the caveat that this recommendation should be revisited as new data become available. In similar fashion, the authors of the Cochrane analysis also recognized that myocarditis is a complex entity and pointed out that some patients seem to have dramatic response to IVIG. Because it is not possible to identify which patients are likely to respond, many cardiologists recommend IVIG in all patients with presumed myocarditis.

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**Key Points**

- Patients with acute myocarditis often present with vague symptoms not clearly referable to the cardiovascular system. Therefore, one must keep a high index of suspicion when caring for patients with viral symptomatology.
- The true incidence of acute myocarditis is unknown. For this reason, definitive determination of outcome is not possible.
- The pathobiology of acute myocarditis is complex and not completely understood. There are ill-defined virus and host factors that determine the severity of the disease course.
- The development of chronic, dilated cardiomyopathy is a common sequela of the acute infectious process.
- An elevated troponin level may support the diagnosis of myocarditis, but a normal troponin level does not exclude the diagnosis.
- Myocarditis should be suspected in patients presenting with ischemic-type chest pain.
- Echocardiography is an essential part of the evaluation of a patient with suspected myocarditis.
- Prehospital care should include rapid transport of the child to the emergency room since inotropic support and possibly extracorporeal support may be required.
- Myocarditis should be suspected in any patient that presents with new onset congestive heart failure or arrhythmia.
Cutting Edge

It is clear that the Dallas criteria, which are based exclusively on the degree of inflammatory infiltrate and myocyte necrosis, may underestimate the presence of immune related myocardial dysfunction. In a randomized placebo-controlled study, Wojnicz defined myocarditis as the upregulation of human leukocyte antigen (HLA) on myocytes obtained by endomyocardial biopsy. Eighty-four patients out of a cohort of 202 had evidence of upregulation of human leukocyte antigen. These 84 patients were randomized prospectively to immunosuppression or placebo. Although the rate of death, transplantation, and hospitalization were not significantly different between the patients receiving immunosuppressive agents and placebo-treated patients, those receiving immunosuppressive agents had an increase in their ejection fraction from 24% to 36%. The placebo group had no significant change. Based on Dallas criteria alone, only 8.3% of the patients studied would have been diagnosed with myocarditis and an additional 19% with borderline myocarditis. The authors concluded that immunosuppressive therapy is likely to be helpful if ongoing inflammation is detected by immunohistochemistry on the basis of upregulation of HLA.

Frustaci also demonstrated the beneficial effects of immunosuppressive therapy in adult patients with new-onset cardiomyopathy and histologic evidence of active lymphocytic myocarditis. Out of 652 biopsied patients, 112 had a histologic diagnosis of myocarditis; 41 of the 112 were characterized by progressive heart failure despite conventional therapy and were treated with immunosuppression (azathioprine and prednisone). Approximately half of the patients responded to immunosuppressive therapy. Responders increased their ejection fraction from 26% to 47% and demonstrated resolved myocarditis on followup biopsies. The 20 nonresponders had progressive deterioration to dilated cardiomyopathy, with 5 deaths and 3 cardiac transplantations. Anti-cardiac antibodies were demonstrated in 90% of those who had responded. Those that did not respond had no evidence of anti-cardiac antibodies.

Disposition

All patients with suspected myocarditis should be admitted to the hospital for observation. Patients with severely decompensated heart failure or hemodynamically significant arrhythmia including atrioventricular block should be admitted to the intensive care unit, ideally in an institution with the capability to provide mechanical circulatory support (Table 3).

Table 3. Admission Criteria For Intensive Care Setting

- Severely decompensated heart failure
- Worsening renal function
- Altered mentation
- Dyspnea at rest
- Hemodynamically significant arrhythmia

Case Conclusion

Your patient is transferred to the Cardiac Intensive Care unit. He fails initial attempts at medical management and is placed on ECMO. The following day, the service is notified that blood, rectal, and nasopharyngeal specimens are all positive for enterox viral ribonucleic acid (RNA) as determined by polymerase chain reaction (PCR).

The patient remains on ECMO for 5 days, is successfully weaned and decannulated on day 6, and is ultimately discharged from the hospital after a few weeks. He has regular cardiology follow-up for mild residual left ventricular dysfunction, though he remains asymptomatic and is growing well.

Summary

With variable presentation patterns, intricate pathobiology, and unproven therapeutic options, acute myocarditis remains an enigmatic disease. In the future, further definition of the cellular level processes and genetic factors that determine the clinical phenotype of individual acute heart failure patients may allow for specific therapeutic targets in certain patient populations. However, in the current era, therapeutic options remain generalized and largely supportive in nature.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.

1. Rosenberg HS, McNamara DG: Acute Myocarditis in Infancy and
1. Of the following viruses, which is most commonly implicated as a cause of acute myocarditis?
   a. Enterovirus
   b. Herpesvirus
   c. Rhinovirus
   d. Rotavirus
   e. Respiratory syncytial virus (RSV)

2. The pathobiology of acute myocarditis is well-defined and completely understood.
   a. True
   b. False

3. Which of the following best describes the role of troponins in the diagnosis of myocarditis?
   a. It is used to differentiate those patients with true myocardial ischemia from those of myocarditis
   b. It is not as accurate as CK-MB in detecting patients with myocarditis
   c. It is useful to exclude the diagnosis when normal
   d. If elevated it can support the diagnosis of myocarditis

4. Which of the following best describes the utility of PCR in the diagnosis of myocarditis?
   a. A positive serum PCR conclusively identifies the causative agent
   b. A positive viral PCR from endomyocardial biopsy conclusively identifies the causative agent
   c. PCR has no role in the diagnosis of myocarditis
   d. A negative serum PCR conclusively excludes myocarditis

5. What is the role of echocardiography in the evaluation and management of myocarditis?
   a. The echocardiogram can provide conclusive evidence of the diagnosis and differentiate myocarditis from other forms of cardiomyopathy
   b. Echocardiography has no role in the diagnosis of myocarditis
   c. Echocardiographic evidence of left ventricular dilation and decreased myocardial function can direct the management
   d. Echocardiography can identify vegetation which support the diagnosis of myocarditis

6. All the following regarding myocarditis are true EXCEPT:
   a. Patients may present with a history of a recent viral illness
   b. It is a common diagnosis in pediatric emergency room malpractice claims
   c. Endomyocardial biopsy should be performed in all patients with suspected myocarditis
   d. Patients presenting with fulminant myocarditis may require extracorporeal support

7. All of the statements below are supported by published guidelines EXCEPT:
   a. Immunosuppressive therapy may play a role in the treatment of myocarditis
   b. Immunoglobulin should be administered to all children with suspected myocarditis
   c. BNP levels should be evaluated in all patients presenting with acute decompensated heart failure
   d. Endomyocardial biopsy should only be considered in patients who fail to respond to conventional therapy

8. All of the following are indications for admission to a pediatric intensive care unit EXCEPT:
   a. Tachypnea without evidence of low cardiac output
   b. Hemodynamically significant arrhythmia
   c. Altered mental status
   d. Congestive heart failure

9. All of the following can indicate significant inflammatory changes of the cardiac conduction system EXCEPT:
   a. Complete atrioventricular block
   b. Atrial tachycardia
   c. Ventricular tachycardia
   d. Sinus tachycardia

10. All of the following findings support the diagnosis of myocarditis EXCEPT:
    a. Elevated troponin
    b. Left ventricular dysfunction on echocardiography
    c. Preceding flu-like illness
    d. Tachycardia out of proportion to illness in an anxious child

11. Which subset of myocarditis patients are most likely to respond to immunosuppressive agents?
    a. Enterovirus
    b. Those with connective tissue disorder
    c. Parvovirus
    d. HIV

12. Chagas disease should be considered in patients with a history of travel to Asia.
    a. True
    b. False

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**Date of Original Release:** April 1, 2008. **Date of most recent review:** March 10, 2008. **Termination date:** April 1, 2011.

**Accreditation:** This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACME) through the joint sponsorship of Mount Sinai School of Medicine and Pediatric Emergency Medicine Practice. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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**Needs Assessment:** The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

**Target Audience:** This enduring material is designed for emergency medicine physicians, physician assistants, and nurse practitioners.

**Goals & Objectives:** Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medico-legal pitfalls for each topic covered.

**Discussion of Investigational Information:** As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that are outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. Disclosure of Off-Label Usage: This issue of Pediatric Emergency Medicine Practice discusses no off-label use of any pharmaceutical product.

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In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Mazer, Dr. Salerno, Dr. Goldman and Dr. Lampell report no significant financial interest or other relationship with the manufacturer(s) of any commercial product.

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**Hardware/Software Requirements:** You will need a Macintosh or PC with Internet capabilities to access the website. Adobe Reader is required to download archived articles.

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**Relative Weight of Evidence Used to Develop The Heart Failure Society of America Practice Guidelines**

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Clinical Evidence</th>
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<tbody>
<tr>
<td>Level A (strongest evidence)</td>
<td>Randomized, controlled clinical trials • May be assigned on the basis of results of a single trial</td>
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<tr>
<td>Level B</td>
<td>Cohort and case-control studies • Posthoc, subgroup analysis, and meta-analysis • Prospective observational studies or registries</td>
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<tr>
<td>Level C (weakest evidence)</td>
<td>Expert opinion • Observational studies — epidemiologic findings • Safety reporting from large-scale use in practice</td>
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