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Myocarditis And Pericarditis In The Pediatric Patient: Validated Management Strategies

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Abstract

Myocarditis and pericarditis are inflammatory conditions of the heart commonly caused by viral and autoimmune etiologies, although many cases are idiopathic. Emergency clinicians must maintain a high index of suspicion for these conditions, given the rarity and often nonspecific presentation in the pediatric population. Children with myocarditis may present with a variety of symptoms, ranging from mild flu-like symptoms to overt heart failure and shock, whereas children with pericarditis typically present with chest pain and fever. The cornerstone of therapy for myocarditis includes aggressive supportive management of heart failure, as well as administration of inotropes and antidysrhythmic medications, as indicated. Children often require admission to an intensive care setting. The acute management of pericarditis includes recognition of tamponade and, if identified, the performance of pericardiocentesis. Medical therapies may include nonsteroidal anti-inflammatory drugs and colchicine, with steroids reserved for specific populations. This review focuses on the evaluation and treatment of children with myocarditis and/or pericarditis, with an emphasis on currently available medical evidence.

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CME Objectives

Upon completion of this article, you should be able to:

1. Identify common presenting signs and symptoms of myocarditis and pericarditis in children.
2. Determine the appropriate diagnostic testing for suspected myocarditis and pericarditis in children.
3. Identify management strategies for myocarditis and pericarditis in children.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

A previously healthy 4-year-old boy with symptoms of chest pain, difficulty breathing, and fever is brought to the ED. His parents note that the symptoms started 1 week prior, and they are flu-like, with general malaise, muscle weakness, and episodes of vomiting. His fever started 3 days prior to evaluation, and he has developed a cough with progressive difficulty breathing over that time, as well. The child points to the left mid-chest when asked about his pain. In triage, he is noted to have a heart rate of 180 beats/min and normal blood pressure for age. He is febrile to 38.8°C, has a respiratory rate of 38 breaths/min, and an oxygen saturation of 91% breathing room air. On examination, you note a pale, ill-appearing child. You auscultate crackles in the bilateral lung bases and a gallop rhythm on cardiac examination, although heart sounds are somewhat diminished. Capillary refill is sluggish. His liver edge is palpable 3 cm below the costal margin. What are the first steps in the immediate management of this patient? What diagnostic workup should be performed? Are there any indications for immediate echocardiography and/or immediate cardiology consultation? What is the appropriate disposition for this patient?

A previously healthy 12-year-old girl presents to your ED with chest pain and fever. Her chest pain has progressively worsened over the last 5 days, and it is described as stabbing. The pain is located over the middle of her chest, without radiation, and it is improved by sitting upright and leaning forward. Fever has been present for the past 2 days and has not resolved with antipyretics. In triage, the patient had an episode of vomiting. Her vital signs are: axillary temperature, 39°C; heart rate, 120 beats/min; normal blood pressure for age; respiratory rate, 30 breaths/min; and oxygen saturation, 96% on room air. On examination, the child appears to be in significant pain. Her pulmonary examination is unremarkable. On cardiac auscultation, you appreciate a friction rub with audible heart sounds. There is no murmur or gallop rhythm, and capillary refill time is normal. She has mild tenderness in the epigastrium. What historical features and examination findings raise concern? What are the initial steps in management of this child? What diagnostic workup should be performed? What is the appropriate disposition for this patient?

Introduction

Myocarditis is an inflammatory disease of the myocardium, occasionally extending to the epicardium and pericardium, which can lead to nonischemic dilated cardiomyopathy (DCM) and chronic heart failure.[1] There are many causes of myocarditis, though a systemic viral illness is most commonly implicated.[2] Presentation can be acute, subacute, or progressive/chronic.[3] Initial presentation often includes a prodromal flu-like illness, including respiratory and gastrointestinal symptoms.[2] Specific symptoms may include cough, dyspnea, vomiting, myalgias, and significant tachycardia out of proportion to the degree of fever.[4] More-severe cases may also present with heart failure, ventricular dysrhythmia, myocardial infarction, new-onset heart block, or cardiogenic shock.[2] Given the variable presentation and disease course, a high index of suspicion is required.

Pericarditis is an inflammatory disease of the pericardium, and it often presents with fever and chest pain.[5,6] Mild cases are likely often self-limiting, so the incidence, especially in children, is unknown. More-severe cases can progress to pericardial effusion, pericardial constriction, recurrent pericarditis, or cardiac tamponade.[6,7] The underlying etiology of pericarditis is quite variable and most commonly includes infection, malignancy, and rheumatologic conditions.[6,7]

This issue of *Pediatric Emergency Medicine Practice* provides an evidence-based approach to the evaluation and management of myocarditis and pericarditis in the pediatric patient, with an emphasis on recent advances in diagnosis and treatment.

Critical Appraisal Of The Literature

A literature review was performed using the keywords *myocarditis* or *pericarditis* in Ovid MEDLINE® and PubMed, focusing on children aged 0 to 18 years. Well-designed randomized controlled trials and prospective and retrospective studies were included. Commonly referenced pediatric and adult studies, as well as historical publications, were also included. A search of the Cochrane Database of Systematic Reviews yielded 4 relevant publications, which were primarily comprised of adult studies.[8-11] The websites of the American Heart Association (AHA) (www.heart.org) and the American Academy of Pediatrics (AAP) (www.aap.org) were searched for guidelines pertaining to myocarditis or pericarditis in children, and none were found. Commonly cited guidelines related to the diagnosis and management of pericardial diseases, published in 2004 by the European Society of Cardiology® (ESC) and revised in 2013, were reviewed.[1,12,13] Canadian Cardiovascular Society (CCS) guidelines on the management of heart failure in children were also reviewed,[14] as were other commonly cited guidelines related to the management of children with myocarditis.[15,16] We identified 1 position statement from the ESC Working Group on Myocardial and Pericardial Disease pertaining to the evaluation of myocarditis.[1]

The literature on pediatric myocarditis mainly consists of case reports and series, small retrospective and prospective studies, and small randomized controlled trials, with primary outcome measures including death, transplant-free survival, and/or improvement in cardiac function. Larger well-designed randomized controlled trials are lacking, which is,

in part, attributable to the rarity of such cases in the pediatric population as well as to discrepancies in the diagnosis of myocarditis.[17] Myocarditis has historically been diagnosed using the Dallas criteria, which include pathologic evidence of inflammation and myocyte necrosis on endomyocardial biopsy samples.[18] However, several studies have shown that the Dallas criteria are insufficient in many cases, even with adequate biopsy samples.[19,20] As a result, many studies include "presumed" myocarditis or DCM, which may lead to the inclusion of etiologies distinct from myocarditis.[4,21-24]

Early literature on pediatric pericarditis predominantly consists of case reports describing specific infectious and systemic etiologies, with a paucity of robust studies. The literature has since shifted to focus on the role of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).[12,13,25-28] More-recent investigation has focused on the use of colchicine for recurrent pericarditis. In 2013, Imazio et al published a randomized controlled trial among adults and showed that 4 patients would need to be treated with colchicine in addition to conventional NSAID therapy in order to prevent 1 episode of recurrence.[29] A subsequent Cochrane Review concluded that there is moderate-quality evidence that the addition of colchicine to NSAID therapy significantly reduces recurrence.[8] The data for colchicine use in children with recurrent pericarditis remains limited to 1 small retrospective study and case reports.[27,30,31]

Etiology And Pathophysiology

Myocarditis

There are numerous causes of myocarditis, both infectious and noninfectious. **(See Table 1.)** In the United States, the most common etiology is viral or postviral infection. Many different viruses are known to cause or be associated with myocarditis, with coxsackievirus, adenovirus, parvovirus B19, and human herpesvirus 6 among the most commonly reported pathogens.[32,33] Over the last 20 years, there has been a shift in the most frequently identified viruses in patients with myocarditis, from adenoviruses and enteroviruses (such as coxsackievirus B) to human herpesvirus 6 and parvovirus B19.[34] Other infectious causes to be considered include bacterial, fungal, spirochetic, rickettsial, protozoal, and parasitic. Chagas disease (caused by the protozoan *Trypanosoma cruzi*) is a frequent etiology of myocarditis and cardiomyopathy in patients from rural Central and South America.[35] Noninfectious etiologies include autoimmune diseases, drug reactions, and hypersensitivity reactions.

The current understanding of the pathophysiology of myocarditis is based largely on murine studies of viral myocarditis and involves a 3-phased course.[2,3,34,36,37] The first (or acute) phase is direct injury to the myocardial cells. Viruses enter the myocytes and active replication leads to myocardial necrosis, while exposure of cellular antigens and activation of the innate immune system cause further damage. This acute stage lasts just a few days. Phase

Table 1. Etiologies Of Myocarditis[34,38]

Etiologies	Causes	
Infectious	Viral	Enteroviruses (coxsackie, echovirus, polio), adenovirus, influenza, parvovirus B19, Epstein-Barr virus, cytomegalovirus, varicella virus, respiratory syncytial virus, hepatitis C, human herpesvirus 6, herpes simplex virus, human immunodeficiency virus, measles, mumps, rubella, dengue fever, yellow fever, chikungunya, Junin virus, Lassa fever virus, rabies, variola virus
	Bacterial	*Staphylococcus, Streptococcus, Meningococcus, Mycobacterium tuberculosis, Klebsiella, Corynebacterium diphtheria, Haemophilus influenzae, Salmonella, Chlamydia, Gonococcus, Mycoplasma, Brucella*
	Protozoal	*Trypanosoma cruzi, Toxoplasmosis, Entamoeba, Leishmania*
	Fungal	Histoplasmosis, Coccidiomycosis, Blastomycosis, *Candida*, Actinomycosis, *Aspergillus*, *Cryptococcus,* Mucormycosis, *Nocardia, Sporothrix*
	Parasitic	*Ascaris, Echinococcus,* visceral larva migrans, *Taenia solium, Trichinella spiralis, Schistosomiasis*
	Rickettsial	*Rickettsia ricketsii, Rickettsia tsutsugamushi, Rickettsia typhi, Coxiella burnetii*
	Spirochetal	*Borrelia burgdorferi, Leptospira, Treponema pallidum*
Autoimmune	Giant-cell myocarditis, lymphofollicular myocarditis, Kawasaki disease, systemic lupus erythematosus, rheumatic fever, inflammatory bowel disease, celiac disease, rheumatoid arthritis, sarcoidosis, scleroderma, dermatomyositis, polymyositis, Churg-Strauss syndrome, hypereosinophilic syndrome, thyrotoxicosis, myasthenia gravis, granulomatosis with polyangitis, Takayasu arteritis, diabetes mellitus	
Toxicity and hypersensitivity	Drugs	Chemotherapeutic agents, sulfonamides, isoniazid, phenytoin, amphetamine, cocaine, anthracyclines, interleukin-2, lithium, digoxin, tricyclic antidepressants, cephalosporins
	Other	Radiation, scorpion bite, bee sting, spider bite, snake bite, copper, lead, iron, arsenic, carbon monoxide, electric shock

2 (or the subacute phase) is characterized by autoimmune reactions mediated by virus-specific T cells targeting host myocytes due to molecular mimicry, as well as by cytokines and antibodies to both viral and cardiac proteins. At this point, cardiac contractile function may decrease. During this phase, which lasts weeks to months, the initial pathogen is either cleared, the immune reaction settles, and cardiac function returns to normal, or the autoimmune process continues, leading to ongoing myocyte damage. The third, or chronic phase, is then characterized by the development of dilated cardiomyopathy.

Fulminant myocarditis is a distinct entity characterized by the sudden (< 3 days) onset of cardiogenic shock and is more commonly seen in infants.[39,40] In a retrospective review of 11 pediatric patients with fulminant myocarditis, 9 patients (82%) were aged < 18 months.[40] This condition requires aggressive hemodynamic support initially—though these patients actually have an excellent long-term prognosis, with significantly lower rates of death or cardiac transplant than patients with acute, subacute, or chronic myocarditis.

Other specific types of myocarditis include giant-cell and eosinophilic myocarditis. Giant-cell myocarditis is primarily autoimmune in nature and often presents with ventricular tachycardia, acute heart block, and rapidly progressing clinical deterioration. Eosinophilic myocarditis is seen in conditions with systemic eosinophilia, and it presents with congestive heart failure, endocardial and valvular fibrosis, and endocardial thrombi. Both conditions should be treated with early corticosteroids.[2]

Pericarditis

Causes of pericarditis are either infectious or noninfectious, although 40% to 85% of cases are idiopathic.[41] **(See Table 2.)** It is thought, however, that many idiopathic cases are actually viral in origin,[6] and a viral etiology is often presumed if the patient had a recent upper respiratory tract infection, exudative effusion, responded to NSAID treatment, or did not have a recurrence.[38] When an infectious etiology is found, viral infection is the most common, followed by bacterial causes.[12] Bacterial pericarditis is also called purulent pericarditis, though an organism is usually not identified. In a retrospective study of 18 children, 6 out of the 18 (33%) had an identifiable organism, with *Staphylococcus aureus* identified in 5 children and *Streptococcus pneumoniae* identified in 1 child.[42] Another retrospective study of 43 children also found *S aureus* to be the most commonly identified bacterial pathogen in 17 out of 43 cases (40%).[43] Noninfectious causes of pericarditis include autoimmune disease, malignancy, radiation therapy, metabolic and endocrine diseases, trauma that penetrates the pericardium, and postpericardiotomy syndrome. Infiltration of the pericardium by granulocytes and lymphocytes marks the inflammation in pericarditis,[38] which then causes increased vascular permeability, local vasodilation, and leakage of protein and free fluid into the pericardial space.[44] This buildup of pericardial fluid increases the pressure in the pericardial space, and subsequently impedes diastolic filling, raises pulmonary pressures, and compromises cardiac output. When severe, systolic blood pressure falls as cardiac tamponade develops.[38]

Differential Diagnosis

Children with acute myocarditis often present with nonspecific symptoms, such as respiratory distress or a flu-like illness. Therefore, common causes of respiratory and gastrointestinal illness should be

Table 2. Etiologies Of Pericarditis[12,38]

Etiologies	Causes	
Infectious	Viral	Enteroviuses (coxsackie, echovirus, polio), adenovirus, parvovirus B19, rubella, influenza, Epstein-Barr virus, varicella, human immunodeficiency virus, mumps
	Bacterial	*Staphylococcus, Streptococcus, Meningococcus, Mycobacterium tuberculosis, Haemophilus influenzae, Salmonella, Mycoplasma, Tularemia, Listeria monocytogenes*
	Protozoal	Toxoplasmosis
	Fungal	Histoplasmosis, Actinomycosis
	Parasitic	*Echinococcus*
	Rickettsial	*Coxiella burnetii*
	Spirochetal	*Borrelia burgdorferi, Leptospira, Treponema pallidum*
Autoimmune	Systemic lupus erythematosus, rheumatic fever, rheumatoid arthritis, granulomatosis with polyangitis, sarcoidosis, systemic sclerosis, Reiter syndrome, ankylosing spondylitis, scleroderma, polymyositis, Churg-Strauss syndrome, Sjögren syndrome, Behçet syndrome, giant cell arteritis, thrombotic thrombocytopenic purpura	
Metabolic and endocrinologic	Uremia, thyroid disease, chylopericardium	
Hematologic and oncologic	Malignancy (primary and metastatic), bleeding diathesis, radiotherapy	
Other	Idiopathic, trauma (penetrating or blunt), postsurgical, iatrogenic (catheter related), pancreatitis, Stevens-Johnson syndrome, Familial Mediterranean fever, Loffler syndrome	

considered while maintaining a high index of suspicion for more-serious etiologies. According to the CCS, myocarditis should be considered in any pediatric patient presenting with a viral prodrome and nonspecific respiratory or gastrointestinal symptoms associated with cardiovascular abnormalities, such as tachycardia, hypotension, or dysrhythmia.[14]

Children with fulminant and giant-cell myocarditis often present with overt heart failure or cardiovascular collapse.[40,45-47] Sudden cardiac death and various cardiomyopathies may present similarly.[34] These include hypertrophic cardiomyopathy and DCM phenotypes. Myocardial infarction, coronary artery anomalies, underlying congenital heart disease, and cardiac tumors should also be considered.

Consider various etiologies of shock, including septic shock, when evaluating children with cardiovascular symptoms. Depending on the clinical scenario, specific infectious etiologies may be considered. Failure to respond to intravenous fluid therapy should prompt consideration of cardiogenic shock and myocarditis. Children presenting with dysrhythmias should be evaluated for possible exposures/ingestions or primary conduction abnormalities.

Children with pericarditis commonly present with chest pain, fever, and gastrointestinal symptoms. Children with evidence of impaired circulation or concerning physical examination findings (friction rub, muffled heart sounds) should be evaluated for pericardial effusion and tamponade physiology. Common causes of pericardial effusion in children are shown in **Table 3**.

Children with underlying respiratory disorders, such as asthma or cystic fibrosis, may present with chest pain, and pneumothorax should be considered in such patients. Pulmonary embolism may present with chest pain, impaired circulation, and/or respiratory symptoms, including hypoxemia. Pulmonary infarction may also present similarly, particularly in children with a history of sickle cell disease. Children with recent cardiac or thoracic surgery may develop chest pain and pleurisy associated with postpericardiotomy syndrome.[12] Specific infectious and autoimmune etiologies should be considered, based on the clinical history.[12]

Table 3. Common Etiologies Of Pericardial Effusion In Children[48]

- Malignancy (including chemotherapeutic drugs)
- Idiopathic etiology
- Autoimmune/collagen/vascular
- Renal disease
- Bacterial
- Human immunodeficiency virus
- Trauma/postsurgical

Prehospital Care

Initial prehospital care should be focused on first stabilizing the patient's circulatory status, then the airway and breathing, as recommended by the AHA in its updated 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. (These guidelines are available at: http://circ.ahajournals.org/content/122/18_suppl_3.toc) The patient should be placed on cardiac monitoring and pulse oximetry. Supplemental oxygen should be delivered when hypoxia is present. Field intubation or bag-valve-mask ventilation, if prehospital personnel are not able to intubate, should be considered in cases of respiratory failure. Depending on the severity of illness, consider transfer to a pediatric facility with advanced cardiac life support (eg, cardiovascular surgery and extracorporeal membrane oxygenation [ECMO]). Obtain peripheral venous access in cases of suspected shock. If peripheral venous access is difficult or cannot be obtained, then clinicians should quickly obtain intraosseous access.

Emergency Department Evaluation

Primary Survey

The initial evaluation of children with suspected myocarditis or pericarditis should include a focused assessment of the child's circulation, airway, breathing, and mental status. Pediatric Advanced Life Support algorithms and emergent procedures, such as intubation, should be utilized as indicated.[49] Attempt to obtain peripheral venous access. If this is unsuccessful, obtain intraosseous access. Point-of-care cardiac ultrasound should be used to evaluate cardiac function and to assess for the presence of pericardial effusion that may require immediate drainage. Early consultation with a pediatric cardiologist is warranted in all cases.

Perform Pericardiocentesis For Cardiac Tamponade Or Large Pericardial Effusion

Patients who present with cardiac tamponade or large pericardial effusions with hemodynamic instability should undergo emergent pericardiocentesis.[50] **Table 4 (see page 6)** presents indications for pericardiocentesis. Place the patient supine at a 30° to 45° angle to horizontal, and sterilize the precordium with povidone-iodine solution before draping. Infiltrate 1% lidocaine 1 to 2 cm below and slightly to the left of the xiphoid process. Attach a 2.5-inch or 3.5-inch 18-gauge spinal needle to a 20-mL to 50-mL syringe, and insert it through the incision at a 45° angle directed cephalad towards the left scapular tip. Maintain negative pressure as the syringe is advanced.

The use of point-of-care cardiac ultrasound

during this procedure is supported by the American College of Emergency Physicians, and it has been shown to facilitate positioning, result in fewer complications, and increase procedural success compared to a blind approach.[51-53] The electrocardiogram (ECG) tracing should be monitored for ectopic beats. ECG monitoring can also be performed by placing a wire with alligator clips on the spinal needle at one end and a precordial lead clip at the opposite end.[50] ST-segment elevation indicates that the needle is in contact with the myocardium. If this occurs, withdraw the needle and redirect it to obtain pericardial fluid. If continued drainage is required, the Seldinger technique may be used to insert a flexible wire through the needle, followed by an end-hole catheter passed over the wire.

Acute complications are shown in **Table 4**.[50,54] In a review of 51 pericardial drainage procedures in 46 patients, Gibbs et al reported an overall complication rate of 15%, with the most common being ventricular puncture.[54] A retrospective study of 73 pediatric patients demonstrated that the complication rate can be reduced to 1% to 3% with the use of point-of-care ultrasonography.[52] First-time success rate using the subxiphoid approach is approximately 90%.[54]

History

Myocarditis typically presents with a bimodal age distribution in infancy/early childhood (age < 2 years) and midadolescence (age 14-18 years), as shown in a retrospective study of 514 children.[55] The clinical presentation varies widely from nonspecific viral symptoms to heart failure, cardiovascular collapse, and sudden death.[2,45,56] Infants, in particular, may present with nonspecific symptoms compared to older children who may be able to verbalize their symptoms.[57] Infants are also more likely to present with fulminant myocarditis and require cardiovascular and/or respiratory support.[40] In a retrospective study of 62 children with myocarditis or DCM, the most common presenting symptoms included shortness of breath (69%), vomiting (48%), poor feeding (40%), upper respiratory symptoms (39%), fever (36%), and lethargy (36%).[4] Freedman et al noted similar presenting symptoms in a review of 31 children presenting to the ED with definite or probable myocarditis, with the most common symptoms being respiratory distress (68%), lethargy (39%), and fever (30%).[58] Of those 31 children, 57% were initially diagnosed with pneumonia or asthma, and 77% of the children had a history of preceding illness.[58] Shu-Ling et al noted in their review of 39 children with myocarditis that only 15 (38.5%) were correctly diagnosed on initial presentation.[33]

Chest pain is a hallmark of pericarditis and is often described as stabbing, worse when lying flat, and improved with leaning forward.[50,59] Children commonly present with a constellation of chest pain, fever, and tachypnea.[60,61] In a retrospective review of 22 children with acute pericarditis unrelated to recent cardiac surgery or an underlying medical condition, the most common presenting symptoms included chest pain (95%), fever (55%), and vomiting (32%).[28] Constrictive pericarditis typically presents with signs of right-sided heart failure, such as jugular venous distension or increased jugular venous pressure, hepatomegaly, dependent edema, or decreased apical impulse.[38] Children with purulent pericarditis typically present with signs of shock.[62]

Past medical history should be reviewed for autoimmune disorders, congenital heart disease, previous cardiac surgeries, immune disorders or recent use of immunosuppressive drugs, malignancies, and trauma. Immunization status, including influenza, should be reviewed. Recent travel history and family history of inherited disorders should be obtained.

Table 4. Indications For Pericardiocentesis And Possible Complications[50,54]

Indications	
Emergent	• Cardiac tamponade
Elective	• Large pericardial effusions (typically > 10-20 mm) • Suspected purulent pericarditis • Malignant pericarditis
Complications	
Acute	• Myocardial penetration • Dysrhythmia • Hemopericardium • Pneumothorax • Coronary artery or vein laceration • Diaphragmatic perforation • Puncture of the peritoneal cavity • Vasovagal episode
Delayed	• Pericardial leakage • Cutaneous fistula • Pericardioperitoneal fistula • Slowly developing pneumothorax • Pneumopericardium • Infection • Peritonitis • Hemorrhagic pericardial effusion

Physical Examination

Children with myocarditis are typically ill-appearing and present with tachycardia out of proportion to the degree of fever.[50] Tachypnea, cyanosis, and hypoxia may also be present. Assess for signs of heart failure, such as crackles/rales, gallop rhythm, hepatomegaly, and peripheral edema.[50,58] In children with pericarditis, physical examination findings may include tachycardia, pericardial friction rub, and muffled heart sounds. A friction rub is heard best at the left lower sternal border while the patient is leaning forward, and it is thought to be pathognomonic for pericarditis.[6] Friction rubs are typically

present with small pericardial effusions, whereas muffled heart sounds are present with large effusions.[38] Children with large pericardial effusions are at risk for developing tamponade characterized by Beck triad of jugular venous distension, muffled heart sounds, and hypotension for age.[6] Pulsus paradoxus, noted by a fall in systolic blood pressure by > 20 mm Hg during inspiration, is associated with tamponade.[38,50] Many consider a fall in systolic blood pressure > 10 mm Hg to be highly suggestive of tamponade physiology.[50] A narrow pulse pressure, defined as the difference between systolic and diastolic blood pressures, is often present as diastolic filling is further compromised with tamponade.

Diagnostic Studies

Given the often nonspecific symptoms associated with myocarditis, a broad array of studies may be obtained. Most children with pericarditis have a self-limited course and do not require an extensive workup. The initial workup should focus on identification of pericardial effusion or tamponade and screening for specific infectious, autoimmune, thyroid, or renal etiologies.[13] Ultimately, the workup should be individualized for each patient based on the presenting history and physical examination.

Myocarditis

Electrocardiography

A 12-lead ECG is recommended for every patient with suspected myocarditis, and it is the single most useful screening test.[1] Although there are no specific ECG findings, abnormalities are seen in the majority of patients. In a retrospective review of 52 patients with myocarditis or DCM, Durani et al found that 100% of children had an abnormality on ECG.[4] Similarly, in a retrospective study of 31 children, Freedman et al found that 93% of patients with definite or probable myocarditis had abnormalities on ECG.[58] The most common abnormalities include sinus tachycardia, ventricular hypertrophy, low-voltage QRS, and inverted T waves.[4,58] Other abnormalities include heart block and atrial or ventricular dysrhythmias.[2,4,58,63] ST-segment elevation may be seen and is often concave in comparison to the convex changes seen in myocardial infarction.[1] **(See Figure 1.)**

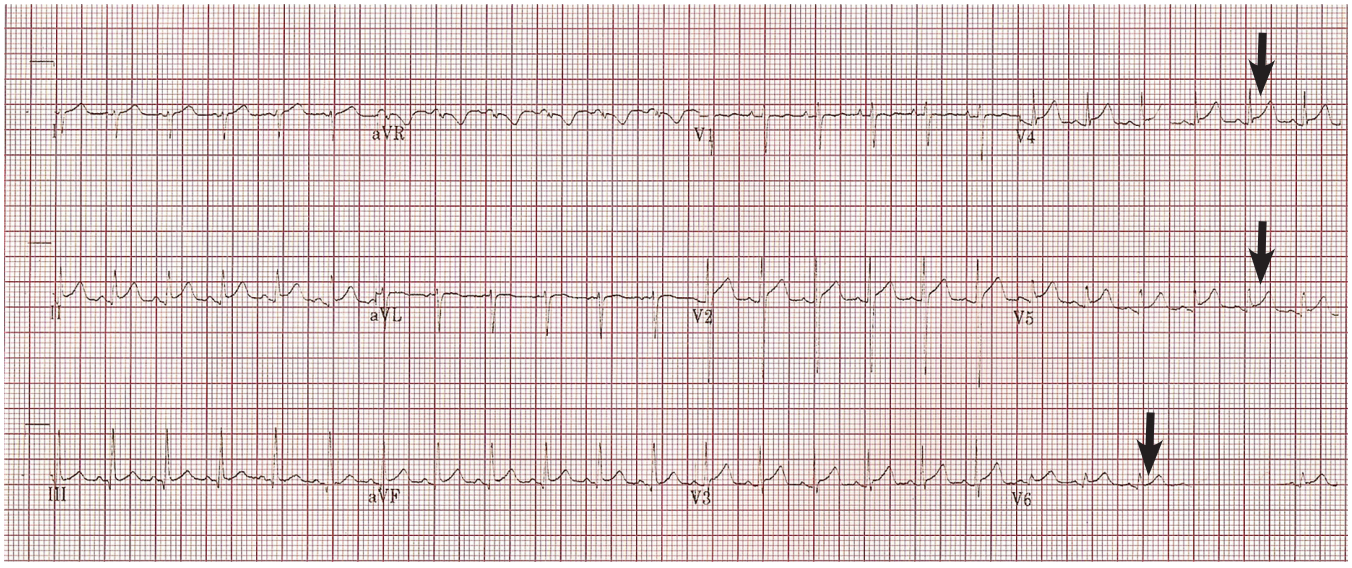
Chest Radiography

Although often normal in children with myocarditis, chest radiography is recommended as a first-line study in all children with suspected myocarditis, since abnormalities may suggest a cardiac etiology.[14] When combined with an abnormality on ECG, the likelihood of a cardiac etiology increases. Freedman et al found that 29 out of 31 children with myocarditis (97%) had an abnormality on either ECG or chest radiography.[58] Common findings include cardiomegaly, pulmonary venous congestion, or pleural effusion.[4,33,58] In a retrospective review of 39 patients with definite or probable myocarditis, 60% of children had an abnormality on chest radiography. The most common abnormality was cardiomegaly, which was seen in 43% of children.[33]

Troponin

Troponin testing is recommended in all cases of suspected myocarditis, as it is often elevated above reference ranges.[1,14,28,64,65] However, the test sensitivity depends highly on the reference cut-off value. In

Figure 1. Concave ST-Segment Increases In Lateral Leads (V_4-V_6) In Myocarditis



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a prospective study of 43 children with myocarditis, DCM, or congenital heart disease, Soongswang et al found troponin T to be significantly more elevated among patients with myocarditis compared to patients without myocarditis, with a sensitivity of 71% and a specificity of 86% when using a cut-off value of 0.052 ng/mL.[65] Eisenberg et al reviewed the cases of 221 children without pre-existing heart disease who had a troponin T level sent for suspected myocarditis. Myocarditis was identified in 18 cases, and all had a positive troponin using a cut-off value of 0.01 ng/mL, with a sensitivity of 100% and a specificity of 85%. The calculated negative predictive value was 100%, with a positive predictive value of 37%.[64]

Inflammatory Markers

White blood cell (WBC) count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often elevated, but they lack sensitivity and specificity in diagnosing myocarditis and pericarditis.[3,4,14,34] However, they may help distinguish inflammatory from noninflammatory illnesses, and they are recommended in all patients with suspected myocarditis.[1]

Echocardiography

Although point-of-care ultrasound performed by an emergency clinician can be used to assess for pericardial effusion and overall cardiac function, formal echocardiography should be obtained in all patients.[1,14] Acute and chronic myocarditis often presents with global left ventricular or biventricular dysfunction, dilated cardiomyopathy, and reduced left ventricular ejection fraction (LVEF).[1] Other abnormalities include wall motion abnormalities, hypertrophic or restrictive cardiomyopathy, or pericardial effusions.[1,66] Echocardiography may also be useful to distinguish myocarditis from valvular causes of heart failure, or myopericarditis, which typically presents with pericardial effusion.[1]

Additional Studies

A number of additional studies may be obtained in the ED after consultation with a pediatric intensivist and/or cardiologist.

Microbiologic Studies

Although blood cultures are of low diagnostic yield, they should be obtained early in the course of illness in patients presenting with signs of shock or decompensated heart failure. Viral studies often do not identify a specific pathogen, and they are not routinely recommended. In a prospective study of 124 adult patients, only 5 (4%) had serologic evidence of viral infection with the same pathogen identified on endomyocardial biopsy.[67] The authors found that the sensitivity of viral serology was 9% with a specificity of 77%, and the positive predictive value was 25%, with a negative predictive value of 49%.[67]

Brain Natriuretic Peptide

Although brain natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) are often elevated,[68] negative tests do not exclude disease, and are, therefore, not routinely recommended.[69] In a review of 19 children with parvovirus-B19-associated myocarditis, BNP was elevated in all 12 children in whom it was tested.[70] In a study of 10 children, Mlczoch et al found that NT-proBNP levels were significantly more elevated in patients with acute myocarditis compared to patients with dilated cardiomyopathy.[71]

Elevated BNP levels may also help distinguish cardiac causes from pulmonary causes of respiratory distress. In a prospective study of 49 infants and children presenting with respiratory distress, BNP levels were significantly higher in patients with a history of congestive heart failure compared to patients with chronic pulmonary disease (pneumonia, bronchiolitis, or asthma).[72]

Other Laboratory Investigations

The CCS recommends routine laboratory investigations, including electrolytes, glucose, renal function, transaminases, thyroid studies, and a complete blood count, in part to rule out other etiologies that may present similarly to myocarditis.[14] In a retrospective review of 31 children with myocarditis, Freedman et al found that aspartate aminotransferase was elevated in 79% of children with definite myocarditis and in 92% of children with probable myocarditis, which was greater than any other laboratory study.[58]

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) is a noninvasive imaging technique that can be used to assess ventricular size, LVEF, wall thickness, and signs of local and global tissue injury, and it may be used to guide endomyocardial biopsy.[16,73] However, cardiac MRI findings have yet to be validated in children, and, thus, MRI is not routinely recommended.[1,14]

Endomyocardial Biopsy

Endomyocardial biopsy remains the diagnostic gold standard for myocarditis.[1] However, the increasing availability of noninvasive studies and sampling error from focal areas of infiltrate going undetected has led to a decrease in the reliance on biopsy results for diagnosis.[19,20,38,55]

The addition of viral PCR studies to endomyocardial biopsy has enhanced the sensitivity.[74] In a review of 34 children, Martin et al showed that 26 out of 34 myocardial biopsy samples (76%) were positive for a viral pathogen based on PCR, and 13 of these samples had no pathologic evidence of myocarditis.[75] Endomyocardial biopsy is not recommend in infants weighing <10 kg or in hemodynamically unstable patients.[14]

Pericarditis

Electrocardiography

An ECG should be obtained on every child with suspected pericarditis,[12,13] and abnormal ECG findings have been seen in 90% to 100% of patients.[28,44] ECG findings typically progress through 4 stages, although multiple stages may be evident at once: (1) concave ST-segment elevation in leads I, II, III, aVL, aVF, and V_2-V_6 with ST-segment decrease in aVR and PR depression throughout (PR depression may be the only finding); (2) ST-segment normalization and T-wave flattening; (3) diffusely inverted T waves; and (4) return to baseline ECG.[13,38,76] **(See Figure 2.)**

Diffuse low-voltage QRS and electrical alternans may indicate a pericardial effusion with tamponade,[13] which are reversible findings after pericardiocentesis.[12,77] Atrioventricular block may indicate underlying Lyme disease.[13] In constrictive pericarditis, ECG findings typically demonstrate low-voltage QRS and nonspecific ST-segment changes.[6]

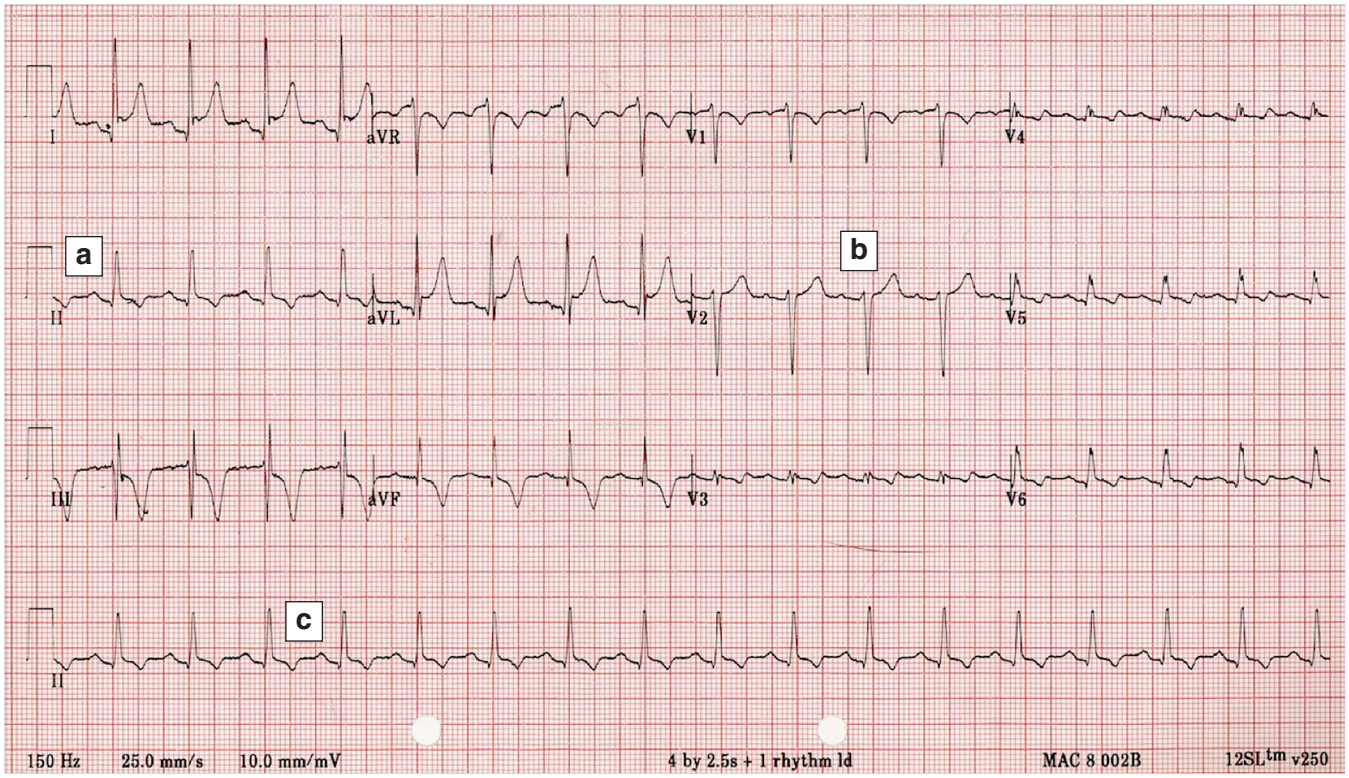
Chest Radiography

Chest radiography is recommended for all patients with pericarditis.[12,13] Findings may include cardiomegaly, particularly if a large pericardial effusion is present (called the "water bottle sign"), or calcifications in constrictive pericarditis.[12,13,38] Chest radiography also identifies associated pulmonary pathology, including pleural effusion, pulmonary infiltrates, or mediastinal enlargement.[12,13] In a retrospective review of 22 children presenting to the emergency department with acute pericarditis, 8 out of 22 patients had a normal chest radiograph (36%), 9 had cardiomegaly (41%), and 5 had pulmonary and/or mediastinal pathology (23%).[28]

Troponin

Troponin elevation is indicative of pericardial or myocardial involvement, and obtaining troponin levels is recommended in all patients.[5,12,78] In a retrospective review of 22 children, troponin I was found to be elevated in 13 of the 15 patients (86%) in whom a level was checked, although a cut-off value was not reported.[28] In 2 prospective adult studies, troponin I elevation (cut-off value of 1.5 ng/mL) was seen in 32% to 49% of patients with pericarditis, and it was more commonly elevated in younger patients and among patients with ST-segment changes on ECG.[79,80] Similar results have been found with tropo-

Figure 2. Electrocardiogram Demonstrating Concave-Up ST-Segment Elevation And PR Depression With Diffuse T-Wave Inversion In Acute Pericarditis



a. PR depression (can occur throughout all leads)

b. Concave-up ST-segment elevation (can occur throughout most of the limb leads (I, II, II, aVL, aVF) and the precordial leads (V_2-V_6)

c. T-wave inversion (diffuse throughout all leads)

Used with permission from Life In The Fast Lane (lifeinthefastlane.com).

nin T. In a prospective study of 105 adult patients with pericarditis or myopericarditis, troponin T was elevated in 61% of patients using a cut-off value of 0.1 ng/mL, and it was more commonly elevated in younger patients.[81]

Inflammatory Markers

Although WBC, CRP, and ESR are often elevated, negative results do not exclude pericardial disease. In a retrospective review, Ratnapalan et al found that CRP was elevated in 100% of children, ESR was elevated > 30 mm/h in 61% of children, and WBC was elevated in 27% of children with pericarditis.[28] Leukopenia may be present and should raise concern for an underlying autoimmune etiology.[13] Inflammatory markers may help distinguish an underlying etiology and are recommended for all patients.[12,13]

Echocardiography

Point-of-care ultrasound should be performed on all patients to assess for pericardial effusion and tamponade,[82] particularly among patients with hemodynamic compromise.[7] In a prospective study of 103 adult patients, Mandavia et al reported a sensitivity of 96% and a specificity of 98% when emergency clinicians performed point-of-care cardiac ultrasound using cardiology interpretation as the gold-standard reference.[83] Although there is a high degree of diagnostic accuracy, a negative study does not rule out a small effusion.[38] Echocardiography is also useful for evaluation of ventricular function, wall motion abnormalities, and pericardial thickening in constrictive pericarditis.[12,13,38]

Pericardiocentesis

Pericardial fluid should be evaluated for cell count and differential, glucose, protein, lactate dehydrogenase, Gram stain, bacterial and viral cultures, cytological evaluation, and PCR for specific pathogens.[6] Fibrous and serofibrous pericardial fluid is associated with immune-related pericarditis and with viral pericarditis when lymphocytes predominate.[6,38] Purulent fluid is seen in bacterial pericarditis, and hemorrhagic fluid is seen with trauma, tuberculosis, and malignancy.[6,38]

Additional Studies

A number of additional studies may be obtained in the ED after consultation with a pediatric intensivist and/or cardiologist.

Microbiologic Studies

Blood cultures are often negative,[27,28] and should be obtained as the presenting symptoms warrant. Ratnapalan et al found that blood cultures were negative in all 22 patients in their retrospective review.[28] Specific viral studies are often low yield and are not routinely recommended.[12,13,27,28,41] In the Ratnapalan study, enterovirus in the pericardial fluid was identified in 1 patient based on PCR, and viral studies identified 4 patients with parvovirus (immunoglobulin-G positive, immunoglobulin-M negative, based on serology).[28] In addition, a positive result rarely changes management recommendations.[13]

Brain Natriuretic Peptide

There are limited data to support the evaluation of BNP in patients with suspected pericarditis, and routine evaluation is not recommended.[12,13] In a prospective study of 42 adult patients, NT-proBNP was an independent predictor of progression of pericardial effusion, with a sensitivity of 80% and a specificity of 78%.[84]

Other Laboratory Studies

Evaluation for specific autoimmune or endocrine etiologies should be based on presenting symptoms, patient history, and physical examination. Screening of antinuclear antibody (ANA), renal function, or thyroid studies may be useful if an underlying etiology is clinically suspected.[7,13] In a study of adult patients with idiopathic recurrent pericarditis, ANA was detected in 53 out of 122 patients (43%), but led to a source in < 10% of patients.[85]

Cardiac Computed Tomography/Magnetic Resonance Imaging

Advanced imaging techniques are recommended when a diagnosis is unclear,[12] and they can be used to identify constrictive pericarditis and restrictive cardiomyopathy, loculated and hemorrhagic effusions, myopericarditis, and pericardial thickening (> 2-4 mm).[6,7,12,38,86]

Treatment

Myocarditis

Supportive Therapies – Diuretics, Cardiac Support, And Antidysrhythmic Medications

Early consultation with a pediatric cardiologist is warranted in all cases. Supportive therapy remains the cornerstone of treatment for myocarditis. This includes judicious fluid management with diuretics and cardiac support with inotropes, afterload reduction and beta-blockers as tolerated, and antidysrhythmics.[87] Intravenous fluids should be used with caution, and diuretic use should be initiated as soon as heart failure is suspected. Furosemide, given either by intermittent bolus or drip, is the preferred diuretic.[88]

Although no randomized controlled trials have evaluated inotropic agents in pediatric myocarditis, a retrospective review of 216 children found that milrinone and epinephrine were used in 45% and 35% of patients, respectively.[89] Emergency clinicians should aim to restore myocardial function when initiating vaso-

pressor support. As such, milrinone and dobutamine are thought to be excellent options, as they improve cardiac contractility and provide afterload reduction.[88] Inotropic support can also be attained with epinephrine, norepinephrine, and dopamine. Digoxin should be used with caution in acute disease.[57,88]

Management of dysrhythmias includes medical therapy with intravenous amiodarone or lidocaine as preferred agents.[88,90] However, no randomized studies have evaluated antidysrhythmic agents in pediatric myocarditis. Cardioversion may be necessary if patients progress to unstable tachydysrhythmias. Ultimately, pacemaker or implantable defibrillator placement may be required.[57,88]

Mechanical ventilation and ECMO with or without transition to a long-term ventricular assist device may be necessary in cases that are refractory to conventional supportive measures.[87] Ultimately, patients may progress to require heart transplantation. In a retrospective review of 216 children with myocarditis, Klugman et al found that 16 patients (7.4%) required ECMO, and 4 patients (1.9%) required heart transplant.[89]

Oxygen-carrying capacity should be maximized in patients with compromised cardiac output. This includes administration of supplemental oxygen and possibly packed red blood cell transfusion, particularly if multiple fluid boluses are needed.[88] Anticoagulation with aspirin or warfarin should also be initiated in patients with severely compromised cardiac output or atrial dysrhythmias.[88]

Immunosuppressive Agents

The use of immunosuppression in the treatment of pediatric myocarditis is controversial and is not routinely recommend in the acute phase of illness. The majority of research has focused on corticosteroids, with primary outcome measures including death, transplant-free survival, improvement or resolution of ventricular dysrhythmia, or improvement in cardiac function.[21,22,91-97] In 1995, the Myocarditis Treatment Trial evaluated the efficacy of immunosuppressive agents in adult patients with myocarditis, and the authors found no difference in the mean change in LVEF at 28 weeks or in mortality among patients treated with conventional therapy alone versus conventional therapy plus immunosuppressive agents.[98] However, several small retrospective and prospective studies among pediatric patients have demonstrated improvement in LVEF among children treated with corticosteroids with or without adjunct immunosuppressive agents, such as azathioprine or cyclosporine.[21,22,92,96,97] These results have been supported by 2 small, randomized controlled trials.[21,95]

Two systematic reviews have assessed the benefit of immunosuppression in children with myocarditis. In 2004, Hia et al reviewed 9 studies from 1984 to 2003.[99] Immunosuppressive agents included were prednisone, intravenous immunoglobulin (IVIG), cyclosporine, azathioprine, interferon-alpha, and Orthoclone OKT®3. The odds for improvement with immunosuppression were between 2.7 (95% confidence interval [CI], 0.59-14.21) and 4.33 (95% CI, 0.52-52.23). However, this difference was not statistically significant.[99] A Cochrane review published in 2013 identified 8 randomized controlled trials focusing on the use of corticosteroids for viral myocarditis.[9] Of the 3 pediatric studies included, 1 was in the English language (Aziz et al, 2010). The authors concluded that treatment with corticosteroids does not reduce mortality (risk ratio [RR] 0.93; 95% CI, 0.70-1.24), but may improve LVEF (mean difference 9%; 95% CI, 7.48-10.52).[9] However, the included trials were small, of low quality, and carried moderate to significant heterogeneity in terms of beneficial effects.

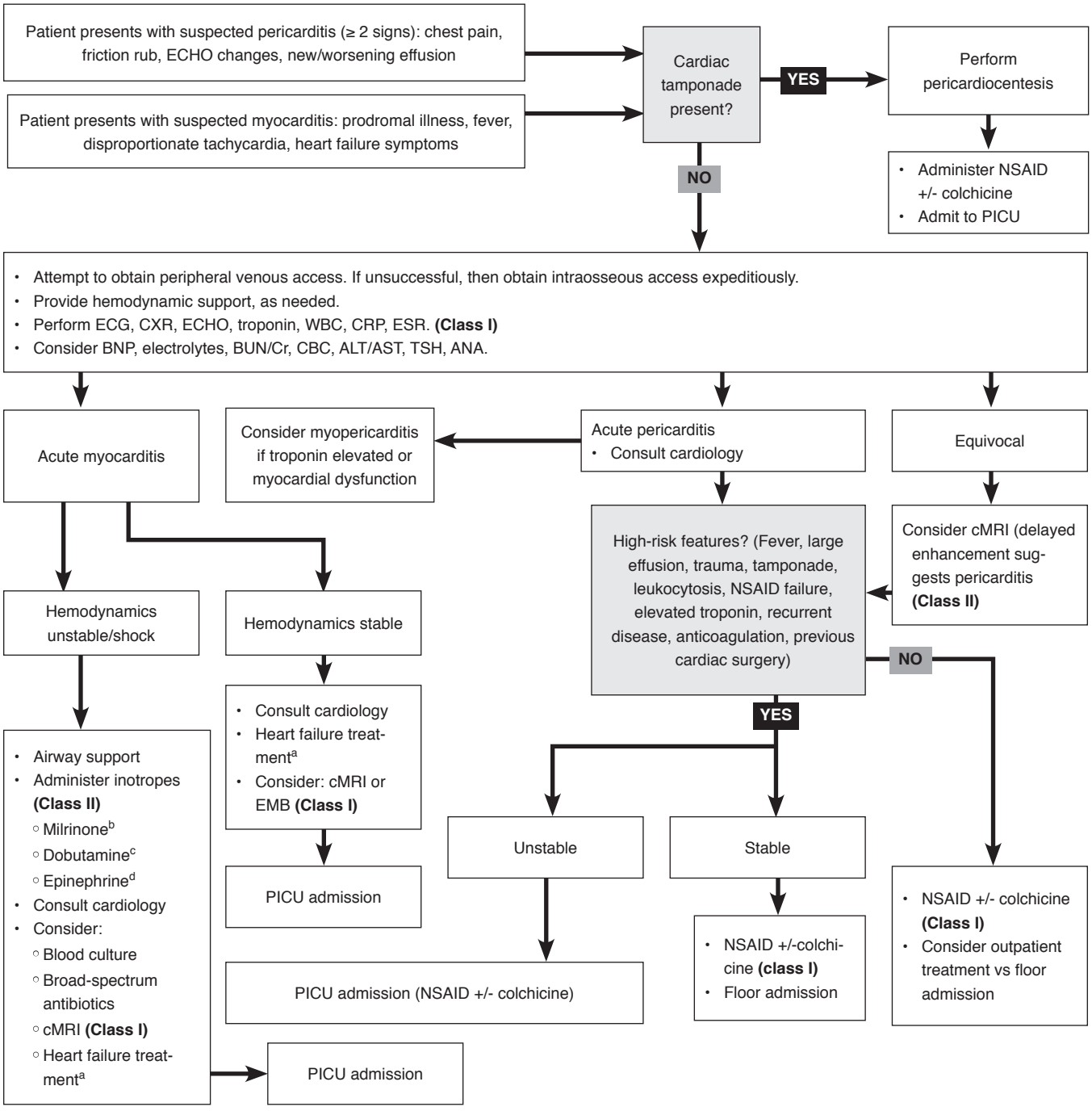
To date, no studies have specifically examined the role of immunosuppression in the management of children with myocarditis in the ED. Given that the acute phase of myocarditis is typically associated with significant infectious burden (ie, viral load), immunosuppressive agents should not be used in cases of active infection and are typically reserved for specific etiologies.

Intravenous Immunoglobulin

Adjunct IVIG therapy for myocarditis is controversial and is not routinely recommended.[11,39,88,100] In 1994, Drucker et al first evaluated IVIG therapy for the treatment of acute myocarditis and demonstrated improvement in left ventricular function at 1 year among 21 children treated with high-dose (2 g/kg) IVIG compared to historical control subjects.[101] In 2009, Hauqe et al retrospectively examined 25 case records of children with a clinical diagnosis of myocarditis who were either treated with IVIG or supportive care only,[102] and they found a significant difference in survival among patients treated with IVIG (92%) compared to patients receiving supportive care (54%).[102] However, a larger retrospective study of 216 children failed to show an increase in survival regardless of illness severity.[89] Similarly, a controlled trial of the use of IVIG evaluated 62 adult patients with idiopathic DCM or myocarditis treated with IVIG compared to placebo albumin infusion, and they found no difference in LVEF at 6 and 12 months.[23] A subsequent Cochrane review conducted in 2005 failed to find sufficient evidence supporting the routine use of IVIG.[11] There are currently no randomized controlled trials assessing IVIG therapy in pediatric myocarditis.

Several studies have examined the use of steroids in combination with IVIG. In 2004, English et al retrospectively studied 41 children with either biopsy-confirmed myocarditis or clinical myocarditis.[103] In their analysis, there was no difference in time to recovery of cardiac function among patients treated with steroids alone, steroids combined with

Clinical Pathway For Emergency Management Of Myocarditis And Pericarditis In The Pediatric Patient



[a]Heart failure treatment consists of judicious fluids, diuretics, beta blockers, afterload reduction
[b]Load 50 mcg/kg over 15 min, followed by 0.5 mcg/kg/min
[c]2.5–15 mcg/kg/min
[d]0.1–1.0 mcg/kg/min

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CBC, complete blood count; cMRI, cardiac magnetic resonance imaging; Cr, creatinine; CRP, C-reactive protein; CXR, chest radiograph; ECG, electrocardiogram; ECHO, echocardiogram; EMB, endomyocardial biopsy; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug; PICU, pediatric intensive care unit; TSH, thyroid stimulating hormone; WBC, white blood cell.

For Class of Evidence definitions, see page 13.

IVIG, or neither treatment.[103] In 2010, Kim et al retrospectively studied 33 children with clinical myocarditis treated with IVIG alone or in combination with steroids, and they found no difference in 1-year survival or recovery of left ventricular function.[104]

Antivirals And Antibiotics

Specific antiviral therapy should be initiated in cases where a treatable viral cause has been identified. Acyclovir has been useful in cases of myocarditis associated with Epstein-Barr virus and varicella.[105-107] However, antiviral therapies are not typically used in the acute phase of disease, as patients typically present with heart failure. Antiviral therapy may be more useful in chronic myocarditis with viral persistence.[108] Although bacterial myocarditis is relatively rare, bacterial cultures should be drawn, and broad-spectrum antibiotic therapy should be initiated when patients present with signs of hemodynamic compromise.[108]

Myocarditis Treatment Summary

The mainstay of treatment for pediatric myocarditis includes hemodynamic support with inotropic agents, judicious intravenous fluids and diuresis with furosemide, and antidysrhythmic control with amiodarone or lidocaine. Corticosteroids and adjunct immunosuppressive agents are not recommended in the acute phase of illness, although their use in later phases may hasten improvement in LVEF. Used alone or in combination with corticosteroids, IVIG is not routinely recommended. Antivirals should be reserved for specific viral etiologies, if known. Antibiotics should be given to patients presenting with undifferentiated shock.

Pericarditis

Supportive Therapies And Nonsteroidal Anti-Inflammatory Drugs

The mainstay of treatment for pericarditis is supportive therapy, and the majority of patients have a self-limited course. Initial treatment should be aimed at reduction of pericardial inflammation and associated chest pain as well as identification of pericardial effusion and tamponade.[13] In many cases, no specific underlying etiology is identified and patients are presumed to have a viral cause. If a specific cause other than viral infection is identified, therapy should be directed toward the underlying etiology.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely accepted as first-line treatment in viral and idiopathic pericarditis, although their use is based largely on consensus and expert opinion from the 2013 ESC guidelines[12,13] and small retrospective studies in children.[27,28] In a retrospective review of 22 children, 68% of whom had idiopathic pericarditis, Ratnapalan et al noted that all children symptomatically improved with NSAIDs.[28] The majority of children in this study were treated with ibuprofen, while others were treated with naproxen, indomethacin, or acetylsalicylic acid.

To date, there are no studies comparing different NSAIDs for the treatment of pediatric pericarditis. The ESC guidelines recommend ibuprofen as the preferred first-line NSAID, due to its beneficial effect on coronary blood flow and its low side-effect profile.[12,13] Ibuprofen should be given in weight-based dosing, up to 800 mg every 6 hours.[12,13,109] Indomethacin and acetylsalicylic acid are acceptable alternatives depending on the clinical situation and concern for side effects.[12,13,109,110] Gastrointestinal protection with proton-pump inhibitors should be considered.

Colchicine

The evidence for colchicine use in pediatric pericarditis is based on several case reports and case series.[27,30,31] In 1998, Yazigi et al first described its use in 3 children with viral or idiopathic pericarditis that was initially unresponsive to NSAIDs and/or corticosteroids.[31] None of the patients had residual pain or effusion on echocardiogram obtained up to 18 months after initiation of therapy at 0.5 mg/day dosing.[31]

Among adults, there is strong evidence that colchicine prevents recurrent pericarditis. In 2013,

Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Imazio et al published a multicenter double-blinded trial of 240 patients randomized to receive either colchicine (at a dose of 0.5 mg/day for patients weighing < 70 kg) or placebo in addition to standard therapy with ibuprofen or acetylsalicylic acid.[29] The addition of colchicine to NSAID therapy conferred a relative risk reduction of 0.56 (95% CI, 0.30-0.72), with 20 out of 120 patients in the colchicine group (16.7%) having recurrent or incessant disease, compared to 45 out of 120 patients in the placebo group (37.5%). The authors calculated that 4 patients would need to be treated with colchicine, in addition to NSAID therapy, in order to prevent 1 episode of recurrence.[29] A 2014 Cochrane review of 4 randomized controlled trials with 564 adult patients found moderate-quality evidence that colchicine in addition to NSAID therapy reduced the number of additional episodes of pericarditis in patients with recurrent disease (hazard ratio 0.37; 95% CI, 0.24-0.58) and reduced recurrence at 18 months in patients presenting with acute disease (hazard ratio 0.40; 95% CI, 0.27-0.61).[8] The updated 2013 ESC guidelines recommend the addition of colchicine in acute pericarditis at a loading dose of 1 mg by mouth twice a day, followed by 0.5 mg daily, if the patient weighs < 70 kg, or 0.5 mg twice a day, if the patient weighs > 70 kg.[13]

Corticosteroids

Low-dose corticosteroids (0.25-0.5 mg/kg/day) should be reserved for patients with symptoms that are refractory to NSAIDs, autoimmune or connective tissue disease-related pericarditis, or uremic pericarditis.[12,13] This is primarily due to evidence showing that early corticosteroid use increases the risk of recurrent pericarditis.[26,27,111] To date, the evidence for corticosteroid use in pediatric patients with pericarditis is limited to a small retrospective study and case reports.[27,112] Raatikka et al described 15 children with recurrent pericarditis, and they noted that the mean number of recurrences for patients treated with corticosteroids was 8.3, compared to 4.5 in the nonsteroid group.[27] In a larger randomized controlled trial among 120 adult patients, Imazio et al found that corticosteroid use was an independent risk factor for disease recurrence (odds ratio [OR] 4.30; 95% CI, 1.21-15.25).[26] However, lower corticosteroid doses may still provide benefit among patients with refractory disease. In a retrospective review of 100 adult patients treated with either high-dose prednisone (1 mg/kg/day) or low-dose prednisone (0.25-0.5 mg/kg/day), the patients treated with high-dose regimens had significantly greater disease recurrence, side effects, or hospitalizations (hazard ratio 3.61; 95% CI, 1.96-6.63).[113]

Antivirals And Antibiotics

Although pericarditis is often attributed to viral etiologies, antiviral therapy is not routinely indicated unless a specific and treatable pathogen is identified. Purulent pericarditis is much less common.[28,43] Patients are often ill-appearing on presentation and broad-spectrum antibiotics may be warranted based on the clinical scenario. The most common bacterial etiologies include *Staphylococcus* and *Streptococcus* species, *Meningococcus*, and *Mycobacterium tuberculosis* and *T cruzi* in endemic regions.[28,42,43,114] If possible, therapy should be guided based on available cultures. If a specific pathogen is highly suspected, therapy should be guided appropriately.

Surgical Interventions

The need for surgical intervention will be determined during consultation with the cardiologist or cardiovascular surgeon. Complete or partial pericardiectomy is the treatment of choice for constrictive pericarditis, and it is often performed in cases of purulent pericarditis given the thick, viscous effusion consistency.[42] In a retrospective review of 27 children with either constrictive or inflammatory pericarditis, 24 patients (89%) had complete resolution of symptoms at the 1-year follow-up from pericardiectomy.[59] Similarly, in a retrospective review of 20 children with purulent pericarditis, 9 patients underwent a pericardial window procedure with no recurrence of symptoms after 2 years.[61] Placement of an indwelling catheter after pericardiocentesis may avoid the need for surgical intervention in select cases.[62] Pericardial infusion of streptokinase and urokinase has also been reported as beneficial.[42,62] In a retrospective review of 18 children with purulent pericarditis, 3 underwent intrapericardial infusion of streptokinase with no recurrence of effusion or constriction.[42]

Pericarditis Treatment Summary

Initial treatment measures should focus on the identification and management of pericardial effusion and tamponade. NSAIDs are the mainstay of treatment, with more-recent evidence among adults supporting the addition of colchicine to prevent disease recurrence. Low-dose corticosteroids should be reserved for patients with symptoms that are refractory to NSAIDs, autoimmune-related pericarditis, or uremic pericarditis. Antiviral therapy is not routinely recommended unless a treatable pathogen is known. Antibiotics may be warranted based on the clinical scenario, and they should include *Staphylococcus* coverage. Coverage for specific pathogens, such as *M tuberculosis* and *T cruzi* may be warranted for specific populations. Surgical consultation may be warranted for patients with constrictive, purulent, and/or recurrent pericarditis.

Special Populations

Patients With Congenital Heart Disease Or Recent Cardiac Surgery

Children with a history of congenital heart disease

and recent cardiac surgery may present with post-pericardiotomy syndrome as a result of operative manipulation of the pericardium, and they are at risk for recurrent pericarditis.[59,115] These children may have relatively poor contractility and are at increased risk for dysrhythmia, depending on the underlying cardiac defect. Special attention should be given to oxygen therapy in these patients, as over-oxygenation may lead to pulmonary vasodilation and over-circulation, with subsequent compromise of systemic blood flow. Prompt consultation with a pediatric cardiologist and/or a cardiovascular surgeon should be obtained in such cases.

Patients Taking Immunosuppressive Medications

Children taking immunosuppressive medications on a chronic basis pose a particular therapeutic dilemma. Immunosuppressive therapies, including corticosteroids, may lead to down-regulation of the immune response and increased pathogen load during active myocarditis.[2] Similarly, corticosteroid use increases the risk of disease recurrence in cases of pericarditis.[26,27,111] Although children on chronic corticosteroid therapy may be weaned, this may carry significant clinical risks. Alternatively, immunosuppression plays an important role in therapy for specific etiologies, such as giant-cell myocarditis or eosinophilic myocarditis,[116,117] and pericarditis related to underlying autoimmune diseases.[5,6,109] The use of immunosuppression in children with myocarditis and pericarditis should be individualized to the underlying etiology. In cases of myocarditis, immunosuppression should only be used after endomyocardial biopsy confirms the absence of active disease.[1]

Patients Originating From Or Traveling From Foreign Countries

Maintain a high index of suspicion for specific infectious etiologies of myocarditis and DCM in patients who are recent immigrants or patients returning from foreign countries. In endemic regions, *T cruzi* (Chagas disease) is a parasite that commonly causes both acute myocarditis and chronic DCM.[118] A small number of patients may present with acute febrile illness, but more commonly remain asymptomatic for an extended period until they develop clinical manifestations, such as dysrhythmia or DCM.[118] In a review of 45 children, Rodriguez-Guerineau et al reported that 43 patients (96%) presented in the chronic phase of disease.[119] Although transmission of Chagas disease is limited to regions of South and Central America, disease occurrence is becoming increasingly prevalent in the southern United States due to migration.[35] Recent estimates suggest that approximately 300,000 people in the United States are currently infected, with 10% to 15% (30,000-45,000 people) likely to have associated cardiomyopathy.[35] Many of these are adult patients; however, congenital Chagas disease is estimated to occur in up to 315 births per year in the United States.[35] Treatment options are limited to benznidazole.

M tuberculosis (TB) should be considered in patients on chronic immunosuppression or returning from endemic regions, such as Africa, where TB represents the most common cause of pericarditis.[114] In a prospective study of South African patients presenting with pericardial effusion, Reuter et al reported that TB pericarditis accounted for 162 out 233 cases (69%).[120] Notably, 84 out of the 233 patients (36%) were HIV positive.[120] A primary complication of TB pericarditis is constrictive pathology,[114,121] characterized by a thickened and fibrotic noncompliant pericardium, which typically requires pericardiectomy. In a retrospective review of 44 South African children with TB pericarditis, 12 patients (27%) developed constriction, and 5 of those patients required pericardiectomy.[122] The authors of the study found no difference in the development of constrictive pericarditis among patients receiving steroids in addition to standard therapies versus standard therapies alone.[122] A Cochrane review of 2 randomized controlled trials found lower mortality among patients treated with corticosteroid regimens compared to standard therapies, although the numbers were small (RR, 0.65; 95% CI, 0.36-1.16).[10]

Other Conditions

Children with an underlying neoplastic process, a history of radiation therapy, or infiltrative diseases (such as sarcoidosis or amyloidosis) may present with restrictive cardiomyopathy, characterized by stiff myocardium and resulting in impaired filling and lusitropy.[7] Uremic pericarditis typically occurs when blood urea nitrogen levels are > 60 mg/dL, and it is associated with large pericardial effusions.[7,12] Treatment includes prompt dialysis and initiation of corticosteroids.[7,12] Uremic pericarditis should be differentiated from hemodialysis-associated pericarditis, which is a distinct entity caused by inadequate fluid removal.[12]

Controversies And Cutting Edge

Myocarditis

Recent investigation has focused on derivation of a scoring system to identify children with myocarditis. In a case-control study of children with myocarditis who were compared to children initially diagnosed with myocarditis but later found to have an alternative diagnosis, Chong et al found that 5 factors were highly discriminating of myocarditis: (1) respiratory distress on examination (OR, 21.3; 95% CI, 2.63-172.41); (2) poor perfusion (OR, 11.0; 95% CI, 3.67-32.89); (3) hypotension (OR, 12.6; 95% CI, 3.32-48.08); (4) any ECG abnormality (OR, 43.8; 95% CI, 2.49-

770.31); and (5) any abnormality on chest radiograph (OR, 5.5; 95% CI, 1.93-15.3).[123] The presence of ≥ 3 variables yielded a positive likelihood ratio of 13 (95% CI, 3.31-51.06) and a negative likelihood ratio of 0.35 (95% CI, 0.22-0.55).[123] However, this scoring system has yet to be validated.

Novel therapies for myocarditis include immunomodulators such as interleukins, interferons, and monoclonal antibodies. Their use stems from the hypothesis that overactivation of the immunologic response in acute myocarditis ultimately leads to myocyte inflammation, fibrosis, and chronic DCM.[2] Several case reports and animal studies have shown that various interleukins and interferons may facilitate a beneficial immune response in viral-induced myocarditis and improve LVEF.[124-132] Muromonab, a monoclonal antibody against the cluster of differentiation 3 (CD3) antigen, has also been shown to improve LVEF when added to immunosuppressive therapies.[133]

Another area of recent investigation includes antiviral therapies, such as ribavirin, pleconaril, ganciclovir, cidofovir, and acyclovir, targeted at specific causative organisms. However, such data are limited to case reports, laboratory studies, and animal studies.[105-107,134-137] Vaccines against enteroviruses, including coxsackievirus, are also in development.[88]

Pericarditis

As in myocarditis, recent investigation has focused on immunomodulators for pericardial disease, particularly for corticosteroid-dependent and recurrent pericarditis. In a multicenter retrospective review of 15 patients with recurrent pericarditis, 12 of whom were children, Finetti et al showed that all patients

Risk Management Pitfalls In The Management Of Myocarditis And Pericarditis In Pediatric Patients (Continued on page 17)

1. **"This kid just has gastroenteritis."**
   Myocarditis is a challenging diagnosis to make prior to overt symptoms of heart failure, and a high index of suspicion is required. When symptoms do not fit a typical picture, further consideration should be given to alternate diagnoses. Children with myocarditis often present with a flu-like illness and tachycardia out of proportion to the degree of fever.

2. **"The troponin is negative, so my patient can't have myocarditis."**
   Troponin levels may have sufficient sensitivity to rule out myocarditis, but the test performance depends on the cut-off level defining a positive test. Current evidence suggests that troponin I and T lack adequate specificity in cases of pediatric myocarditis. While a negative troponin is reassuring, emergency clinicians should interpret this result in the context of the cut-off value used at their facility.

3. **"I gave 60 mL/kg of intravenous fluid to a child with myocarditis, and now he's getting worse."**
   Children with myocarditis often present in shock, which prompts aggressive intravenous fluid administration. Failure to respond to an initial fluid bolus should raise concern for a cardiogenic cause, such as myocarditis. In cardiogenic shock, poor cardiac contractility leads to the development of pulmonary edema. Clinically, patients will develop labored breathing and crackles/rales on examination. Treatment should include inotropes and intravenous diuretics, such as furosemide.

4. **"I diagnosed my patient with myocarditis, admitted her to the floor team since she was stable, and didn't consult cardiology."**
   Prompt consultation with a pediatric cardiologist should be obtained in all cases of suspected myocarditis. Admission planning should start early and in conjunction with a pediatric intensivist, as patients can decompensate quickly. If there is no pediatric intensive care unit or cardiovascular intensive care unit at your center, plans for transfer to an appropriate center should be arranged early.

5. **"My patient has myocarditis with signs of hemodynamic compromise. I'll start her on furosemide, and hopefully she'll turn around without inotropes."**
   While diuresis is an essential component of treatment, inotropic support should not be withheld if patients present with signs of hemodynamic instability. Peripheral venous access should be obtained promptly. Providers should aim to restore cardiac contractility when choosing a vasopressor. Milrinone is the agent of choice; however, this may not be available in all emergency departments. Epinephrine is another excellent choice, with the addition of dobutamine, if needed.

treated with an interleukin-1 beta-receptor antagonist (anakinra dosed at 1-2 mg/kg/day) had resolution of symptoms within days, and they were able to successfully wean off other therapies, including corticosteroids.[138]

Finally, IVIG has recently been reported to be effective in cases of recurrent pericarditis. Del Fresno et al reported 2 children with postsurgical pericarditis who had resolution of pericardial effusion after high-dose IVIG therapy given at monthly intervals for a total of 3 months in one case and 5 months in the other.[115]

Disposition

Patients with myocarditis typically present with signs of heart failure, and they often require admission to a pediatric or cardiovascular intensive care unit.[14,55] Patients without overt heart failure or signs of cardiovascular compromise are at risk for precipitous clinical deterioration, and admission to an intensive care unit or capable telemetry floor should be considered.[1] In the event of transfer, patients should be admitted to the nearest center with a cardiac catheterization facility, cardiovascular surgeon, and ECMO capabilities.[1]

Children with pericarditis complicated by tamponade, pericardial effusion requiring pericardiocentesis, or large pericardial effusion also typically warrant admission to a pediatric or cardiovascular intensive care unit. Surgical consultation should be considered if pericardiocentesis is not feasible. Although low-risk adult patients may be treated on an outpatient basis where appropriate services exist,[139]

Risk Management Pitfalls In The Management Of Myocarditis And Pericarditis In Pediatric Patients (Continued from page 16)

6. **"My patient was crashing, and it looked like tamponade. I performed a pericardiocentesis over the anterior chest using a 10-mL syringe and a 22-gauge needle."**
Pericardiocentesis is a potentially life-saving procedure, and knowledge of appropriate technique is critical. Clinicians should quickly sterilize the precordium, just below the xiphoid process. If there is time, local lidocaine should be infiltrated and sedation used as tolerated. A 2.5-inch or 3.5-inch 18-gauge spinal needle should be attached to a 20-mL to 50-mL syringe and inserted at a 45° angle just below and to the left of the xiphoid process, directed towards the left scapular tip. Maintain gentle suction on the syringe while slowly inserting the needle. If promptly available, point-of-care cardiac ultrasound should be used to visualize the procedure. Continuous cardiac monitoring should be used throughout the procedure. Ectopic beats or ST-segment elevation may indicate cardiac irritation from increased needle depth insertion.

7. **"The pericardiocentesis is done, but the patient is getting worse. What could have gone wrong?"**
Complications from pericardiocentesis are common. The most common complication is ventricular puncture, which may lead to hemopericardium. Other complications include dysrhythmia, pneumothorax, coronary artery or vein laceration, diaphragmatic perforation, puncture of the peritoneal cavity, and vasovagal episodes.

8. **"The ECG doesn't show diffuse ST-segment elevation, so my patient can't have pericarditis."**
Diffuse ST-segment elevation occurs in the acute phase of the disease. Children with delayed presentation or recurrent disease may have diffusely inverted T waves or low-voltage QRS complexes.

9. **"Steroids can't hurt, right?"**
Steroids increase the risk for development of recurrent pericarditis, and they are only recommended in refractory cases, or in cases where the underlying medical condition would be treated with such therapy (eg, autoimmune disease, known giant-cell myocarditis, or eosinophilic myocarditis).

10. **"I diagnosed my patient with pericarditis and treated him with high-dose aspirin."**
Ibuprofen is the treatment of choice for acute pericarditis due to the beneficial effects on coronary blood flow and the minimal side-effect profile. Although no pediatric studies have compared different NSAIDs in the treatment of acute pericarditis, aspirin use in pediatric patients should be limited to patients with pericarditis after myocardial infarction or patients with risk of thrombosis.

children with milder illness are typically admitted to a capable telemetry unit for further etiologic workup, evaluation of therapeutic response, and pain control. Adult studies have identified high-risk patients who require admission, including patients with fever, large pericardial effusion or tamponade, failure of NSAID therapy, a malignant or traumatic etiology, suspected myopericarditis, an elevated troponin level with ECG changes, concurrent treatment with immunosuppression or anticoagulation, or patients of female gender.[139-141] Such prognostic indicators have not been evaluated in children, and they should be interpreted with caution if applied to children with pericarditis.

Summary

Myocarditis and pericarditis remain challenging diagnoses for emergency clinicians given the nonspecific presenting symptoms. ECG, chest radiograph, echocardiogram, troponin, inflammatory markers, and early consultation with a cardiologist are recommended in all cases. Children with myocarditis who present with heart failure symptoms should be managed with supportive therapies, including judicious intravenous fluids, diuretics as tolerated, inotropic support, and antidysrhythmic medications. Immunosuppressive therapies should not be used in cases of active myocarditis, and they are typically reserved for known autoimmune etiologies. Children with pericarditis present with chest pain, and they may present with tamponade physiology. Emergency clinicians should be familiar with indications for pericardiocentesis and the associated complications. The mainstay of therapy for pericarditis includes NSAIDs, with more-recent evidence supporting the addition of colchicine. Children with myocarditis or pericarditis should be admitted to a center capable of endomyocardial biopsy and ECMO.

Time- And Cost-Effective Strategies

- All patients with suspected myocarditis or pericarditis should have the following studies performed: ECG, chest radiography, echocardiogram, troponin, and inflammatory markers (WBC, CRP, and ESR). Further laboratory investigation should be guided by presenting symptoms and physical examination findings, or reserved for patients in whom a specific etiology is suspected.
- Although formal echocardiography is recommended for all patients with myocarditis or pericarditis, point-of-care ultrasound can be used as an extension of the physical examination to rapidly identify decreased ventricular function and/or pericardial effusion.
- In cases of myocarditis, early consultation with a pediatric cardiologist is warranted. Admission to a pediatric or cardiovascular intensive care unit should be arranged early, even in mild cases, given the risk of acute deterioration. Patients requiring higher levels of care should be transferred to a facility capable of endomyocardial biopsy and ECMO.
- Failure to respond to intravenous fluids should prompt early consideration of myocarditis. A peripheral venous catheter should be placed for administration of vasopressors and hemodynamic monitoring.

Case Conclusions

You were concerned that your 4-year-old patient had myocarditis with new-onset heart failure. You had the patient moved to a resuscitation room and placed on cardiac monitoring and supplemental oxygen. Two peripheral intravenous lines were placed, and blood cultures were drawn. Laboratory investigations were notable for a metabolic acidosis with normal electrolytes and renal function, and slightly elevated transaminases. Lactate was mildly elevated, and leukocytosis was present with mild anemia. Troponin was elevated above reference range. You gave the patient a normal saline bolus of 20 mL/kg without resolution of tachycardia or improvement in capillary refill. He progressively developed worsening tachypnea and increasing oxygen needs, requiring rapid sequence intubation for impending respiratory failure. The 12- lead ECG showed sinus tachycardia with low-voltage QRS and inverted T waves throughout. You obtained a chest x-ray that showed cardiomegaly with pulmonary vascular congestion. Bedside cardiac ultrasound showed biventricular dysfunction with no pericardial effusion. You gave a dose of intravenous furosemide, and after consultation with cardiology, a formal echocardiogram was obtained. The patient was started on a milrinone drip before admission to the cardiovascular intensive care unit.

After examining your 12-year-old patient, you felt she may have acute pericarditis. You placed the patient on cardiac monitoring, which showed sinus tachycardia with ST-segment elevation. The 12-lead ECG confirmed these findings, with diffuse ST-segment elevation in leads I, II, II, aVL, aVF, and V2-V6, and ST-segment depression in aVR and V1. You placed an intravenous line, and treated her pain with morphine. Laboratory investigations were notable for a negative troponin, mild leukocytosis, and normal electrolytes and renal function. Chest x-ray showed no evidence of cardiomegaly or pulmonary venous congestion. Bedside cardiac ultrasound showed a small pericardial effusion that did not require drainage. You obtained consultation with cardiology, and started her on NSAID therapy. After a period of observation, the patient did not show any signs of hemodynamic instability or tamponade physiology. Formal echocardiogram was obtained prior to transfer to the pediatric floor for further workup of the etiology of her pericarditis.

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 references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.

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1. Which of the following is the most common cause of myocarditis in children?
a. Bacterial
b. Viral
c. Autoimmune
d. Traumatic

2. An 18-year-old adolescent boy presents to the emergency department with dyspnea on exertion, progressive fatigue, and cough. The family recently moved to the United States from rural Argentina. Vital signs are as follows: temperature, 38°C; heart rate, 120 beats/min; blood pressure, normal for age; respiratory rate, 30 breaths/min; and oxygen saturation, 96% on room air. On physical examination, you note no cardiac murmurs. There are crackles at the bilateral lung bases. Chest radiograph shows cardiomegaly with pulmonary venous congestion. You suspect a cardiac etiology, possibly myocarditis. Which of the following is the most likely cause of the symptoms?
a. *Blastomycosis*
b. *Meningococcus*
c. *T cruzi*
d. *Staphylococcus*

3. In which age group is fulminant myocarditis most common?
a. 0-18 months
b. 19 months-36 months
c. 4 years-10 years
d. 11 years-18 years

4. What is the most commonly identified bacterial cause of pericarditis in children in the United States?
a. *M tuberculosis*
b. *Streptococcus*
c. *Staphylococcus*
d. *Meningococcus*

5. Which of the following is NOT commonly seen in the presentation of pericarditis?
a. Fever
b. Vomiting
c. Chest pain
d. Orthopnea

6. Physical examination findings suggestive of cardiac tamponade include all of the following EXCEPT:
a. Hypotension
b. Jugular venous distension
c. Exaggerated friction rub
d. Muffled heart sounds

7. Routine work up for children with myocarditis should include all of the following EXCEPT:
a. ECG
b. Troponin
c. Chest radiograph
d. Viral studies

8. In which manner do ECG changes in pericarditis typically progress?
a. Diffuse ST-segment elevation, normalization of ST, T-wave inversion, low-voltage QRS
b. T-wave inversion, low-voltage QRS, diffuse ST-segment elevation, normalization of ST
c. Low-voltage QRS, T-wave inversion, diffuse ST-segment elevation, normalization of ST
d. T-wave inversion, diffuse ST-segment elevation, normalization of ST, low-voltage QRS

9. Regarding the use of colchicine for acute pericarditis, which of the following is TRUE?
a. Colchicine should only be used for specific etiologies, such as autoimmune pericarditis.
b. Treatment with colchicine reduces episodes of recurrent pericarditis when added to conventional therapy with NSAIDs.
c. Treatment with colchicine should be used in place of NSAID therapy.
d. Colchicine should only be used for pericarditis refractory to other therapies.

10. In which of the following scenarios should corticosteroids be considered for acute pericarditis?
a. A 16-year-old girl with a first episode of acute pericarditis
b. A 2-year-old girl with recent ventricular septal defect repair and small postoperative pericardial effusion
c. A 16-year-old boy with penetrating chest trauma and pericardial effusion
d. A 17-year-old girl with systemic lupus erythematosus and recurrent pericarditis

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