

# Acute viral myocarditis: Diagnosis

Paul A. Checchia, MD; Thomas J. Kulik, MD

**Key Words:** acute viral myocarditis; diagnosis; echocardiography

**T**here are insufficient data to support a diagnostic standard for this topic.

## GUIDELINES

The diagnosis of acute viral myocarditis should be based on a high index of suspicion, attention to historical clues, and a thorough physical exam. These should be augmented by the use of chest radiograph, electrocardiography, echocardiography, and the endomyocardial biopsy.

*Options.* Additional evidence of the diagnosis of acute viral myocarditis may be obtained by measurements of cardiac troponin and the use of cardiovascular magnetic resonance imaging.

## OVERVIEW

The diagnosis of acute viral myocarditis requires a high index of suspicion, attention to historical clues, and thorough physical exam. Regardless of pathogenesis, the diagnosis is based on clinical findings, echocardiographic evaluation, and endomyocardial biopsy sampling. There are, however, limitations to the use of each of these examinations, including sampling errors related to heterogeneity of disease, the invasiveness of the procedure, and inability of the pathologic examination of tissue to reflect the physiologic effect of circulating mediators. A simple, highly sensitive, and specific test that could accurately detect myocyte injury during the course of acute viral myo-

carditis, etiological agent, and response to therapy would be clinically valuable. Unfortunately, no sensitive or specific clinical or laboratory clues to the diagnosis have been found (1).

The diagnosis of acute viral myocarditis starts with ruling out other causes of myocardial dysfunction. In particular, structural cardiac lesions (e.g., left-sided outflow obstruction and anomalous coronary artery) can cause congestive heart failure, especially in the neonate, and need to be excluded using echocardiography. Pericardial effusion is also easy to diagnose. Arrhythmia (especially supraventricular tachycardia and the permanent form of junctional reciprocating tachycardia) can usually be easily eliminated from consideration using the electrocardiogram. Systemic hypertension can present with congestive heart failure. Inherited metabolic causes of myocardial dysfunction may be more difficult to rule out, although a positive family history, long-standing failure to thrive, other abnormalities on physical exam (e.g., hypotonia), and characteristic electrocardiographic (ECG) changes when present (e.g., for glycogen storage disease of the heart) may suggest the need for detailed investigation along those lines.

Having excluded other causes of myocardial dysfunction, there are multiple tests that may lend support to the diagnosis of acute viral myocarditis or offer important information relevant to the therapy provided. This review will concentrate on available approaches to the diagnosis in children. An important distinction must be made regarding the separation of diagnostic vs. prognostic examination and between the more general diagnosis of severe heart failure and the features of shock vs. the specific diagnosis of acute viral myocarditis.

## PROCESS

MEDLINE database searches were conducted to find published data regard-

ing the diagnosis of acute viral myocarditis in children. Of the 255 potentially relevant studies, 28 were evaluated as evidence for this question.

## SCIENTIFIC FOUNDATION

We chose to examine six diagnostic modalities: electrocardiogram, chest radiography, echocardiography, serum markers of myocardial injury, endomyocardial biopsy, and magnetic resonance imaging.

### Electrocardiographic Findings

ECG findings in patients with acute viral myocarditis are highly variable. The most typical findings are: 1) sinus tachycardia; 2) low-voltage QRS in standard (total voltage < 5 mm) and precordial leads and low-amplitude Q waves in the lateral precordial leads; and 3) flattening or inversion of T waves in the standard or L precordial leads. Thirty-one of 45 cases reported by Keith et al. (2) had flattened or inverted T waves.

There are a number of other ECG findings that may be present with acute viral myocarditis. Marked elevation of ST segments is not uncommon. Keith et al. (2) reported that 10 of 45 cases (ages not specified) had such markedly deviated ST segments as to suggest myocardial infarction. These observations were made in patients without confirmation of the diagnosis by echocardiography and myocardial biopsy, but more recent experience is similar. Angelini et al. (3) described 12 adults with symptoms, cardiac enzymes, and ECG findings (ST elevations) suggesting myocardial infarction, with normal coronary arteries and histologic evidence of acute viral myocarditis. There are other reports of ECG and other findings consistent with myocardial infarction in adults with myocarditis (4–6).

Arrhythmia is not uncommon in myocarditis, including supraventricular

From the Divisions of Critical Care Medicine and Cardiology, St. Louis Children's Hospital and the University of Washington School of Medicine, St. Louis, MO (PAC); and the Division of Cardiology, Cincinnati Children's Hospital Medical Center and the University of Cincinnati School of Medicine, Cincinnati, OH (TJK).

Copyright © 2006 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies

DOI: 10.1097/01.PCC.0000244336.60719.8C

tachycardia, atrial ectopic tachycardia, ventricular premature beats, ventricular tachycardia, and ventricular fibrillation (7). Friedman et al. (8) described 12 patients (ten patients <18 yrs old), mostly without obvious myocarditis, who had biopsy findings consistent with myocarditis. Eleven had ventricular tachycardia, and one had multiform ventricular premature beats. Seven still had ventricular ectopy (mostly ventricular premature beats) an average of 50 months after presentation. Wiles et al. (8a) made similar observations. Of 33 patients (31 were ≤18 yrs old) evaluated for ventricular ectopic rhythm (but without findings of pump dysfunction) using endomyocardial biopsy, three had focal lymphocytic myocarditis. Variable degrees of atrioventricular block, including complete heart block, have been well described. For example, Take et al. (6) described nine adults with complete heart block with myocarditis, which was permanent in two cases.

### Chest Radiograph

The cardiac silhouette is generally enlarged with acute viral myocarditis but may be normal in size and configuration. Pulmonary congestion (edema) may be present in variable degrees. Pleural effusion and interstitial infiltrates may also be observed. We are aware of no studies available examining the specific use of the chest radiograph in the diagnosis of acute viral myocarditis.

### Echocardiography

The most characteristic echocardiographic appearance is that of enlarged ventricular end-systolic and diastolic dimensions and of reduced shortening and ejection fractions; atrioventricular valve regurgitation, especially mitral regurgitation, is also common. However, multiple studies of adults with clinically or histologically established acute viral myocarditis have described regional wall motion abnormalities, without global dysfunction or ventricular dilation, in patients with mild disease (9). Indeed, the regional wall motion abnormalities associated with this disease may be highly suggestive of myocardial infarction in adults, although subsequent resolution suggests that true infarction did not occur (10). There seems to be few published data regarding regional wall motion abnormalities in children. Transiently in-

creased ventricular wall thickness has also been observed (11).

Other cardiac ultrasound findings include pulmonary arterial hypertension (related to increased left atrial pressure) and ventricular thrombi. Evidence of restrictive ventricular physiology and dystrophic calcification has been (rarely) described (12, 13).

### Serum Markers of Myocardial Injury

*Myocardial Muscle Creatine Kinase Isoenzyme.* There are limited data on the use of myocardial muscle creatine kinase isoenzyme (CK-MB) in the diagnosis of acute viral myocarditis in children. Data on the utility of CK-MB in myocarditis mainly examine its sensitivity and specificity in comparison with cardiac troponin measurements. Soongswang et al. (14) demonstrated that CK-MB and cardiac troponin T were significantly higher compared with dilated cardiomyopathy and left-to-right shunt with congestive heart failure. In a mixed population of adults and children, Lauer et al. (15) demonstrated a greater sensitivity and specificity of troponin measurements in comparison with CK-MB.

*Cardiac Troponin.* Several investigators have demonstrated elevation of cardiac troponin measurements in patients with suspected acute viral myocarditis (14–18). These investigations have utilized both troponin I and T measurements with equivalent findings. However, these studies have suffered from their lack of consistency in their comparison with histologic findings obtained by biopsy. Soongswang et al. (18) conducted a pediatric specific study to assess the use of serum cardiac troponin T level as a noninvasive indicator to diagnose acute viral myocarditis in children. Pediatric patients with clinically suspected myocarditis or dilated cardiomyopathy and a control group were recruited. History, physical examination, electrocardiogram, chest roentgenogram, echocardiogram, serum cardiac troponin T level, or endomyocardial biopsy and clinical course were studied. The “gold standard” to diagnose acute viral myocarditis was endomyocardial biopsy proved according to the Dallas criteria or recovery from cardiovascular problems within 6 months of follow-up. The population consisted of 43 patients admitted due to cardiovascular problems from primary myocardial dysfunction and retrospectively divided into

three groups: acute viral myocarditis, idiopathic chronic dilated cardiomyopathy, and moderate to large ventricular septal defect with congestive heart failure. Their data show that a serum cardiac troponin T level of 0.052 ng/mL is an appropriate cutoff point to make the diagnosis.

The use of troponin measurements in ongoing low cardiac output states from various pathogeneses of cardiac failure is a separate question from its role in the diagnosis of acute viral myocarditis. What has yet to be examined is the role of troponin in the timing of biopsy and its role in the management of immunosuppressive regimes. It could be a theoretical advantage to time the endomyocardial biopsy coincident with a high troponin level to improve the yield of finding active inflammatory infiltrate.

### Endomyocardial Biopsy

Endomyocardial biopsy remains the standard for diagnosing acute viral myocarditis, despite its known limitations, such as sampling error, procedural complications, variability of pathologic interpretation, and low negative predictive value (19). The standard histologic criteria for establishing the diagnosis (the Dallas criteria (20)) were established in an adult population. Although studies have applied these criteria to pediatric populations, modifications based on age groups have not been found.

The vast majority of available pediatric studies can be described as representing class III evidence. Those that can be classified as class II are six in number. Schmaltz et al. (21) have the largest pediatric experience, reporting on 60 children. They found that biopsies were diagnostic in 11% of cases, helpful in 71%, and of no help in 16%. Additional pediatric experience is reported by Nugent et al. (22) with 24 children, the 26 children reported by Chandra (23), and the 15 children reported by Lewis et al. (24). Each of these reports had similar success in finding the endomyocardial biopsy diagnostic in their populations.

Recent advances in molecular biology techniques are increasing their sensitivity and overall utility. It is now possible to routinely use polymerase chain reaction and ribonucleic acid hybridization to provide rapid, reliable, and specific detection of viral genetic material in biopsy samples. Martin et al. (25) used polymerase chain reaction to analyze 38 myocardial tissue samples from suspected myocardi-

tis patients and 17 control patients. They detected viral genome in 68% of samples from myocarditis patients and none from controls. In addition, blood sampling was negative in all but four cases.

## Magnetic Resonance Imaging

Several noninvasive strategies are emerging as adjunctive diagnostic tests. Antimyosin scintigraphy, contrast-enhanced cardiovascular magnetic resonance imaging, and echocardiographic digital image processing may each be useful for the noninvasive localization and assessment of the extent of inflammation in patients with presumed acute viral myocarditis.

Investigators have evaluated the role of contrast-enhanced cardiovascular magnetic resonance imaging, and several methods have been studied, including contrast enhancement and noncontrast T2-weighted imaging. Gagliardi et al. (26) examined the utility of contrast-enhanced cardiovascular magnetic resonance imaging in a pediatric population and found it aided in the diagnosis when compared with the endomyocardial biopsy. However, advances in imaging techniques have allowed even further improvements of this modality in adult populations examined (27–30). Although each study demonstrated high accuracy for the diagnosis of myocardial inflammation, the variable that should be used as the gold standard for comparison affects the effective interpretation of the data. Some investigators (26) compared imaging with the results of the endomyocardial biopsy, whereas others relied on a combination of clinical, laboratory, ECG, and angiographic findings (27, 29).

## SUMMARY

The diagnosis of acute viral myocarditis must be based on a synthesis of the patient's clinical history, physical examination, imaging studies, and laboratory tests; no single diagnostic modality can suffice. Clinical history, physical exam, and imaging—especially echocardiography—are important for ruling out non-inflammatory pathogenesis that may present in the same way as acute viral myocarditis (e.g., genetic myopathies and structural congenital heart disease). Electrocardiography may help confirm the diagnosis (especially, low voltages in limb and precordial leads and flattening T waves) but can prove confusing; marked

ST-segment elevation (along with elevation in serum cardiac enzymes, and even regional wall motion abnormalities on echocardiography) may occasionally suggest a need to evaluate the coronary arteries, even in patients who ultimately prove to have acute viral myocarditis. Chest radiographic findings are highly variable (ranging from a normal chest radiograph to marked cardiomegaly and pulmonary edema) and nonspecific. Echocardiography is the most readily available means of estimating ventricular dimensions and systolic function, making it exceedingly valuable because myocardial dysfunction (as distinct from arrhythmia) seems to be the most common mode of presentation in children.

CK-MB and troponin I and T have all been found to be elevated with acute viral myocarditis; probably the best data to date regard elevation of troponin I. Endomyocardial biopsy, looking for histologic evidence of inflammation, has served as the gold standard for diagnosis, although it is clearly positive in only a relatively small fraction of patients for whom there is a strong clinical index of suspicion for the disease. Searching for the presence of viral genome in myocardial samples seems to considerably increase the sensitivity of endomyocardial biopsy.

Advanced imaging modalities, such as antimyosin scintigraphy and contrast-enhanced cardiovascular magnetic resonance imaging, may each be useful for the noninvasive localization and assessment of the extent of inflammation in patients with presumed acute viral myocarditis, although they are not yet in widespread use.

## KEY ELEMENTS FOR FUTURE INVESTIGATION

It seems unlikely that more extensive evaluation of the “classic” tests used to help establish the diagnosis of myocarditis (electrocardiography, chest radiography, and two-dimensional echocardiography) would prove to be of much value for enhancing our ability to diagnose this disease. Similarly, given its invasive nature and relative lack of sensitivity (even with viral genome analysis), endomyocardial biopsy is unlikely to increase its utility significantly. It seems more likely that advanced imaging techniques that probe the biology of the myocardium (e.g., antimyosin scintigraphy) will ultimately prove to be the most useful for diagnosis

and, hopefully, for providing prognostic information. The lack of a sensitive and specific gold standard has complicated, and will continue to complicate, rigorous studies of this disease.

## REFERENCES

1. Mason JW, O'Connell JB, Herskowitz A, et al: A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med* 1995; 333:269–275
2. Keith JD, Rowe RD, Vlad P: Heart Disease in Infancy and Childhood. New York, Macmillan, 1978, pp 928–931
3. Angelini A, Calzolari V, Calabrese F, et al: Myocarditis mimicking acute myocardial infarction: Role of endomyocardial biopsy in the differential diagnosis. *Heart* 2000; 84: 245–250
4. Dec GW Jr, Waldman H, Southern J, et al: Viral myocarditis mimicking acute myocardial infarction [see comment]. *J Am Coll Cardiol* 1992; 20:85–89
5. Miklozek CL, Crumpacker CS, Royal HD, et al: Myocarditis presenting as acute myocardial infarction. *Am Heart J* 1988; 115: 768–776
6. Take M, Sekiguchi M, Hiroe M, et al: Long-term follow-up of electrocardiographic findings in patients with acute myocarditis proven by endomyocardial biopsy. *Jpn Circ J* 1982; 46:1227–1234
7. Garson A Jr, Smith RT Jr, Moak JP, et al: Incessant ventricular tachycardia in infants: Myocardial hamartomas and surgical cure. *J Am Coll Cardiol* 1987; 10:619–626
8. Friedman RA, Kearney DL, Moak JP, et al: Persistence of ventricular arrhythmia after resolution of occult myocarditis in children and young adults. *J Am Coll Cardiol* 1994; 24:780–783
- 8a. Wiles HB, Gillette PC, Harley RA, et al: Cardiomyopathy and myocarditis in children with ventricular ectopic rhythm. *J Am Coll Cardiol* 1992; 20:359–362
9. Shirani J, Iltercil A, Chandra M, et al: Cardiovascular imaging in clinical and experimental acute infectious myocarditis. *Front Biosci* 2003; 8:e323–e336
10. Chandraratna PA, Nimalasuriya A, Reid CL, et al: Left ventricular asynergy in acute myocarditis: Simulation of acute myocardial infarction. *JAMA* 1983; 250:1428–1430
11. Hiramitsu S, Morimoto S, Kato S, et al: Transient ventricular wall thickening in acute myocarditis: A serial echocardiographic and histopathologic study. *Jpn Circ J* 2001; 65: 863–866
12. Kimball TR, Witt SA, Marasco LA, et al: A unique echocardiographic presentation of acute myocarditis: Restrictive pathophysiology. *J Am Soc Echocardiogr* 1994; 7:187–189
13. Stallion A, Rafferty JF, Warner BW, et al: Myocardial calcification: A predictor of poor outcome for myocarditis treated with extra-

- corporeal life support. *J Pediatr Surg* 1994; 29:492–494
14. Soongswang J, Durongpisitkul K, Ratanarapee S, et al: Cardiac troponin T: Its role in the diagnosis of clinically suspected acute myocarditis and chronic dilated cardiomyopathy in children. *Pediatr Cardiol* 2002; 23: 531–535
  15. Lauer B, Niederau C, Kuhl U, et al: Cardiac troponin T in patients with clinically suspected myocarditis. *J Am Coll Cardiol* 1997; 30:1354–1359
  16. Briassoulis G, Papadopoulos G, Zavras N, et al: Cardiac troponin I in fulminant adenovirus myocarditis treated with a 24-hour infusion of high-dose intravenous immunoglobulin. *Pediatr Cardiol* 2000; 21:391–394
  17. Sato Y, Yamada T, Taniguchi R, et al: Serum concentration of cardiac troponin T in patients with cardiomyopathy: A possible mechanism of acute heart failure [letter]. *Heart* 1998; 80:209–210
  18. Soongswang J, Durongpisitkul K, Nana A, et al: Cardiac troponin T: A marker in the diagnosis of acute myocarditis in children. *Pediatr Cardiol* 2005; 26:45–49
  19. Mason JW, O'Connell JB: Clinical merit of endomyocardial biopsy. *Circulation* 1989; 79:971–979
  20. Aretz HT, Billingham ME, Edwards WD, et al: Myocarditis: A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987; 1:3–14
  21. Schmaltz AA, Apitz J, Hort W, et al: Endomyocardial biopsy in infants and children: Experience in 60 patients. *Pediatr Cardiol* 1990; 11:15–21
  22. Nugent AW, Davis AM, Kleinert S, et al: Clinical, electrocardiographic, and histologic correlations in children with dilated cardiomyopathy. *J Heart Lung Transplant* 2001; 20:1152–1157
  23. Chandra RS: The role of endomyocardial biopsy in the diagnosis of cardiac disorders in infants and children. *Am J Cardiovasc Pathol* 1987; 1:157–172
  24. Lewis AB, Neustein HB, Takahashi M, et al: Findings on endomyocardial biopsy in infants and children with dilated cardiomyopathy. *Am J Cardiol* 1985; 55:143–145
  25. Martin AB, Webber S, Fricker FJ, et al: Acute myocarditis: Rapid diagnosis by PCR in children. *Circulation* 1994; 90:330–339
  26. Gagliardi MG, Bevilacqua M, Di Renzi P, et al: Usefulness of magnetic resonance imaging for diagnosis of acute myocarditis in infants and children, and comparison with endomyocardial biopsy. *Am J Cardiol* 1991; 68: 1089–1091
  27. Abdel-Aty H, Boye P, Zagrosek A, et al: Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: Comparison of different approaches [see comment]. *J Am Coll Cardiol* 2005; 45:1815–1822
  28. Friedrich MG, Strohm O, Schulz-Menger J, et al: Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis [see comment]. *Circulation* 1998; 97: 1802–1809
  29. Laissy JP, Messin B, Varenne O, et al: MRI of acute myocarditis: A comprehensive approach based on various imaging sequences. *Chest* 2002; 122:1638–1648
  30. Mahrholdt H, Goedecke C, Wagner A, et al: Cardiovascular magnetic resonance assessment of human myocarditis: A comparison to histology and molecular pathology. *Circulation*. 2004; 109:1250–1258