Update on myocarditis in children
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\textbf{Purpose of review}

Myocarditis is an uncommon pediatric illness, and it is frequently missed by medical personnel. It often masquerades as more common pediatric illnesses such as respiratory distress or gastrointestinal disease. Given that myocarditis accounts for 12% of sudden cardiac death among adolescents and young adults, the suspicion of this illness in the differential diagnosis of children presenting with nonspecific symptomatology and disease progression can be lifesaving.

\textbf{Recent findings}

Historically, the diagnosis of myocarditis required endomyocardial biopsy. More recently ancillary diagnostic modalities have been used to help make the diagnosis less invasively. The use of laboratory testing, echocardiography, and cardiac MRI can now make the diagnosis in the absence of invasive biopsy and can help improve the diagnostic yield when biopsy is performed. Additionally, with an improved understanding of the pathophysiology of this disease, research has focused on novel therapeutic interventions such as immunoglobulin therapy and immunosuppressive therapy in the care of the patient with myocarditis.

\textbf{Summary}

Myocarditis is a challenging diagnosis to make. With advent of newer diagnostic modalities and an improved understanding of the disease and its progression, there is a genuine hope that outcomes of pediatric myocarditis will be improved. The first step, however, is for medical providers to consider this entity in the differential diagnosis of patients with concerning presentation or illness history.

\textbf{Keywords}

children, diagnosis, myocarditis, treatment

\textbf{Introduction}

Acute myocarditis continues to be a significant cause of morbidity and mortality among children and young adults in the United States [1]. With an estimated annual incidence of 1 per 100,000 [1–5], this rare disease continues to be implicated in as many as 12% of sudden cardiac deaths among adolescents and young adults [1,6\textsuperscript{**},7,8]. Although myocarditis can be secondary to both viral and non-viral processes, it is thought that the majority of cases of pediatric myocarditis in children in the United States occur due to a viral infection [9–11]. In otherwise healthy patients, the pathophysiology of this disease process involves invasion of the myocardium by inflammatory cells, with or without necrosis of myocytes [9,10,12]. The histological classification, referred to as the Dallas criteria, necessitates an endomyocardial biopsy (EMB) for diagnosis [10,12]. EMB, the ‘gold standard’ test for diagnosis of myocarditis, enables the identification of lymphocytic invasion of cardiac tissue and allows detection of the involved virus by PCR [13,14]. The sensitivity and specificity of biopsy remain poor, however, given that the myocardial inflammation in myocarditis tends to be patchy, making it difficult to biopsy the diseased area of the myocardium [6\textsuperscript{**},15\textsuperscript{**}]. Additionally, there is the potential for substantial inter-observer variation [6\textsuperscript{**},15\textsuperscript{**}].

Myocyte destruction in myocarditis is caused by direct cellular damage by the infectious agent as well as the innate host immune response [9,14]. In other words, as an intact immune system is crucial for clearing the virus-infected cardiac myocytes, it is also the immune response that is partially responsible for the myocytes’ destruction [9]. With persistence of viremia and the accompanying immune response, acute myocarditis can progress to a more chronic dilated cardiomyopathy [9].

Making the diagnosis of myocarditis can be challenging due to its subtle clinical signs and symptoms. The diagnosis of myocarditis should be suspected whenever a child presents with unexplained shortness of breath or fatigue, a new arrhythmia, or acute cardiac failure just following a viral illness [16]. The purpose of this review is to explore
the recent advances that have been made in the understanding, diagnosis and treatment of myocarditis.

**Etiology**

Myocarditis is defined as an inflammatory disease of the myocardium [6**]. It can be the result of viruses, bacteria (i.e. Streptococcus), and parasites (i.e. Trypanosoma cruzi), or drugs such as antracyclines [6**]. As noted earlier, the majority of cases of myocarditis in children in the United States are secondary to a viral infection [9–11] Coxsackie B is the most well known cardiotoxic virus [6**]. However, a number of other viruses have been implicated, including adenovirus, Epstein Barr virus, influenza A and B, human herpes simplex virus type 6, cytomegalovirus and parvovirus [9,17].

Kuhl et al. [17] recently explored the role of parvovirus as a cause of myocarditis and found that often, parvovirus was the inciting agent, endomycocardial biopsies were negative by the Dallas criteria [17]. These specimens were only notable for mild lymphocytic invasion (<10 cells/mm²). What was noted, however, was the predominance of macrophages in these viral specimens. This leads to the postulate that different viruses have different pathologic mechanisms for myocyte destruction (macrophage-dependent vs. lymphocyte-dependent, for example) [13]. Additionally, this lack of lymphocytic predominance on endomycocardial biopsies may suggest an inefficient immune response against the viral pathogen, resulting in ineffective viral clearance [17].

Most recently, Bratincsak and colleagues reported an association between pandemic novel H1N1 influenza A and myocarditis [18**]. In their single institution retrospective review, during October 2009, four children out of the 80 who were admitted with novel H1N1 infection had evidence of myocarditis. Of note, three of the affected children presented with fulminant disease. They concluded, on the basis of this small case series, that novel H1N1 infection may pose a greater risk for the development of myocarditis than other strains of influenza.

The current understanding of myocarditis is that the disease evolves in three phases. In the acute phase of the disease, there is histological evidence of inflammatory cell invasion of the myocardium and subsequent myocardial necrosis and apoptosis [6**]. This initiates the host’s immune cascade, which is described as the subacute phase of the disease. Natural Killer (NK) cells, macrophages and T cells are all involved in the immune cascade [9]. NK cells are believed to be cardioprotective as they are responsible for limiting viral replication [9]. T cells have been largely implicated in the inflammatory response that results in myocardial damage [19,20]. In addition, macrophage activation has been found to lead to the release of cytokines. Murine mouse models of myocarditis have demonstrated that these cytokines are both protective and directly toxic to myocyte [21].

Although the first wave of the immune cascade causes myocyte destruction, it has been found that the most destructive phase of infection occurs approximately 7–14 days following the inoculation, the stage of T-cell invasion [9,22,23]. The proposed mechanism of this second phase of disease is through molecular mimicry such that the T cells nonselectively attack the virus and the virally infected myocytes [9]. This insight has shaped current treatment options, which have focused on immunomodulation and immunosuppressive therapy. These will be further explored below. The third phase of the disease is the healing phase, which is characterized by fibrosis of the involved myocardium [6**]. However, with continued inflammation and persistent viremia, left ventricular dysfunction and dilation may ensue [6**,24].

**Clinical presentation**

The clinical presentation of children with myocarditis varies from asymptomatic cases to those with complete cardiovascular collapse (referred to as acute fulminant myocarditis) [25]. Presentation varies with age [10]. Neonates may present with nonspecific symptoms suggestive of infection including fever, listlessness and poor feeding, or they may present with more ominous signs including apnea, episodic cyanosis, and diaphoresis [10]. Of note, inflammatory infiltrates on cardiac muscle biopsies taken at autopsy from cases of sudden infant death syndrome (SIDS) have demonstrated myocarditis as a cause of death [26]. Krous et al. [27] studied a series of infants who had died of SIDS and noted the presence of scattered inflammatory cells and necrotic cardiomyocytes even in infants who did not have myocarditis. They proposed that this histological finding is likely a normal event in the developing heart exposed to environmental pathogens. They did, however, note that the degree of cardiac infiltration by lymphocytes and macrophages was more extensive in infants who had died of myocarditis.

The clinical presentation of older children and adolescents is also variable. Most children will present with nonspecific respiratory or gastrointestinal complaints; only a minority actually reports chest pain [10]. The nonspecific nature of such symptoms often results in the misdiagnosis of myocarditis [28]. In fact, Durani et al. [29**] recently noted that the most frequently reported signs of myocarditis were nonspecific symptoms such as shortness of breath (69%), vomiting (48%) or poor feeding (40%). The same analysis also noted that the diagnosis of myocarditis was not made on the first presentation to a medical provider in 83% of cases [29**]. Although providers often consider tachycardia without a
clearly defined cause (fever or dehydration) as a clue to the presence of myocarditis [14], Durani et al. [29*] found that 66% of patients with myocarditis in their series actually had normal heart rates at presentation. Additionally, other signs of congestive heart failure were absent in the majority of patients; only 50% had hepatomegaly, and only 34% had abnormal lung examination [28,29**].

**Diagnosis**

Various diagnostic modalities can be used by the medical provider to arrive at the diagnosis of myocarditis.

**Electrocardiogram and chest radiograph**

When there is a suspicion of a myocarditis, most providers will start the evaluation with an electrocardiogram (EKG) and a chest radiograph. EKG abnormalities are noted in anywhere from 93–100% of cases of myocarditis [28,29**]. The most common EKG changes are sinus tachycardia (46%), ST-T wave changes (32–60%), axis deviation (53%), and ventricular hypertrophy (46%) [4,10]. Other possible EKG findings that can be noted are: infarction patterns, decreased ventricular voltages, or atrial abnormalities [28]. Chest radiographic findings have been reported in majority of cases of myocarditis (69–90%), with cardiomegaly being the most commonly reported radiographic finding (56–60%) [28,29**].

**Laboratory investigation**

Freedman et al. [28] found that the most sensitive marker for myocarditis was an elevated aspartate aminotransferase (AST), which was elevated in 85% of definite and probable cases of myocarditis. Others have looked at markers of inflammation, including erythrocyte sedimentation rate and C-reactive protein, and have found that these have been elevated in anywhere from 27–56% of cases [4,10]. The utility of cardiac troponins in the investigation of myocarditis has also been examined. Cardiac Troponin I is a subunit of a thin filament of the contractile apparatus of the myocardium [30*]. Cardiac Troponin T is a contractile protein unique to cardiac muscle cell [31]. These markers are cardioselective and will be released into the blood stream within hours following cardiac muscle cell injury or death [30*,31]. Cardiac Troponin T has been found to be elevated in children with myocarditis. A level of more than 0.052 ng/ml has a sensitivity of 71% and specificity of 86% for pediatric myocarditis [32].

A recent study looked at the incidence of elevated cardiac enzymes among children hospitalized for viral illness. The aim of the study performed by Renko et al. [30*] was to determine the rate of subclinical myocarditis among such patients. Their findings revealed that even among those few patients with elevated cardiac enzymes, these cases were not consistent with myocarditis. Although cardiac enzymes can be helpful markers when a patient has signs and symptoms of myocarditis [33], this marker was not useful in the diagnosis of subclinical myocarditis [30*].

**Echocardiography**

Echocardiography assesses cardiac muscle function and associated valvar insufficiency as well as wall motion abnormalities. Durani et al. [29**] recently showed that in 98% of cases of pediatric myocarditis, the echocardiography would be abnormal, with segmental wall motion abnormalities being the most common findings (hypokinesia, akinesia and dyskinesia) [34].

**Endomyocardial biopsy**

Although EMB is the historical gold standard for the diagnosis of myocarditis, it is invasive and a potentially dangerous procedure, especially in the pediatric patient [35]. The potential complications associated with this procedure include pneumothorax, hemothorax, dysrhythmia, heart block, perforation and death [35]. As a screening tool, EMB is insensitive due to the patchy nature of myocardial inflammation [6**,15**]. When used with concurrent PCR and in-situ hybridization, it allows rapid detection and identification of the viral genetic material [36].

**Noninvasive diagnostic modalities**

Recent interest has focused on the use of noninvasive modalities for the diagnosis of myocarditis. Although echocardiography is helpful in elucidating wall motion abnormalities, cardiac MRI (CMR) can actually detect the often subtle patchy myocardial involvement [22,26]. CMR visualizes the whole myocardium, allowing demarcation of inflammation from later remodeling [10]. It, therefore, not only detects myocarditis, but also quantifies the extent of damage, can be used to guide the execution of the EMB and can be used to monitor lesions [15**,34]. Gadolinium is the contrast agent that is used because it penetrates those cells that have lost their cell membrane integrity and allows diffusion of the contrast agent into the intracellular space [26]. Signal enhancement correlates with myocardial blood flow and edema, which tends to be increased in those tissues that are inflamed [15**,26]. However, on first pass perfusion, CMR features of myocarditis can be missed [34]. It is the delayed enhancement images that allow visualization of the necrotic and fibrotic myocardium [37**], which are largely located in the lateral free wall in cases of myocarditis, localized to the subepicardial and intramyocardial regions [15**,26,34,38].

In a recent retrospective study that looked at the use of CMR in children as a predictor of outcome, Vashist et al. [10,39] found that myocarditis in the pediatric population

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is characterized primarily by subepicardial and transmural enhancement. When CMR has been used to determine outcome, the findings that have been associated with poor outcome have been transmural myocardial involvement, global hypokinesia, left ventricular dilatation, and left ventricular ejection fraction less than 30% [10,39].

On the basis of the strong evidence supporting CMR’s role in the diagnosis of myocarditis, in April 2009 the International Consensus Group on CMR Diagnosis of Myocarditis (Lake Louis Consensus Criteria) proposed the following diagnostic criteria for myocarditis [37**]. In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial inflammation if at least two of the following criteria are present: regional or global myocardial signal increase in T2-weighted images; increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images; at least one focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (‘late gadolinium enhancement’).

A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present. A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if:

1. None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation.
2. Only one of the criteria is present.

**Treatment**

The cornerstones of treatment for myocarditis in children remain supportive, and many patients will recover without long-term cardiac sequelae [11]. However, some will suffer continued cardiac compromise including the development of dilated cardiomyopathy and even sudden cardiac death. In the acute phase of the disease, current practice is to support the patient to the degree needed with inotropes, afterload reduction, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) as the condition warrants [10].

Several investigators have examined the utility of adjuvant therapeutic interventions aimed at preventing long-term cardiac compromise. Intravenous immunoglobulin (IVIG) has been the most common agent studied [11,40]. As noted earlier, an autoimmune response may be responsible for the majority of the myocardial damage [41]; targeting this process should improve outcome [40]. Some reports have demonstrated increased survival among those managed with IVIG therapy and especially among children [11,40,42*]. Drucker et al. [40] found a statistically significant improvement in survival outcomes of pediatric patients with myocarditis treated with high-dose IVIG. McNamara et al. [43] conducted the only randomized control trial to date, among adults, and failed to show improved survival or improved left ventricular function in those patients with myocarditis treated with high-dose IVIG. Additionally, in a recent multicenter study that looked at outcomes of pediatric patients with myocarditis, the use of IVIG did not impart a survival advantage [44*].

Immunosuppressive therapies are possible adjuvants to therapeutic modalities for myocarditis management [45]. Camargo et al. [46] performed the sole randomized control trial to date, which looked at immunosuppressive therapy in children with biopsy proven viral myocarditis. Patients were randomized to treatment arms, but outcomes were not blinded. Patients were randomized to receive prednisone alone, prednisone and azathioprine or prednisone, azathioprine and cyclosporine. The authors of this study concluded that combination immunosuppressive therapy lead to improvement in cardiac outcome [46]. Hia et al. [47] performed a meta-analysis evaluating the current literature on the benefit of immunosuppressive therapy for management of acute viral myocarditis. They determined that, while the odds of improved outcome were noted among patients who received immunosuppressive therapy, the results were not statistically significant [47]. The prevailing consensus is that, in order to conclude that immunosuppressive therapy does in fact impart a survival advantage, a large multicenter randomized control trial is warranted [47].

Beta blockers, specifically carvedilol, have also been investigated in terms of their therapeutic benefit in patients with heart failure. Beta blockers are well known to improve survival in adult patients with congestive heart failure [48**]. A 2009 Cochrane review examined the current evidence for the use of beta blockers in children with congestive heart failure. Three randomized controlled trials with 20, 22 and 161 patients, respectively, were analyzed. Although a therapeutic benefit was noted in the two smaller studies, the larger study failed to demonstrate a statistically significant benefit among those patients with congestive heart failure who received beta-blockers [48*,49].

**Outcome**

Although estimates have suggested that the incidence of myocarditis is approximately 1 per 100 000 [1–5], the true incidence remains largely unknown due to the significant number of cases that go undiagnosed [10]. The outcome of acute myocarditis is, therefore, difficult to characterize [25,50]. Some children will have complete myocardial recovery; some will die, whereas others will progress to
dilated cardiomyopathy with an ultimate requirement for cardiac transplantation [25,51]. According to Greenwood et al.’s [52] 30-year study of outcomes of 161 children with primary myocardial disease (myocarditis, nonobstructive cardiomyopathy and endomyocardial fibroelastosis), nearly a third had full recovery, a third died, and a third had continued cardiac compromise. Patients with acute fulminant myocarditis have a more clearly defined course. They often present with abrupt-onset cardiovascular collapse and require aggressive intensive care management [25]. Despite this, they usually have a favorable long-term survival [25,53]. As Lee et al. [50] noted, those patients who survived beyond 72 h without the need for ECMO had a 97% increased likelihood of survival. Kuhn et al. [16] went on to further describe the clinical features on presentation that were associated with adverse outcomes. Ejection fraction less than 30%, a shortening fraction less than 15% and moderate-to-severe mitral regurgitation were all associated with ultimate development of severe cardiac failure [16].

Conclusion
Myocarditis will continue to challenge medical providers due to its propensity to occur in young and healthy hosts and to masquerade as benign childhood illness. With the advent of new diagnostic techniques and continued research into adjutant therapeutic strategies, morbidity and mortality from this disease can hopefully be lessened.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 370–371).

7 A review of the the utility of computed tomography (CT) and MR as diagnostic modality in the evaluation of conditions associated with sudden cardiac death.
This observational study detailed the MRI findings that are consistent with myocarditis and how this can be used in the evaluation of the patient with signs and symptoms concerning for myocardial infarction.
This important letter to the editor reports on a case series of children who developed myocarditis in association with novel H1N1 infection.
This descriptive study detailed the clinical profiles of patients associated with acute myocarditis and describes how these can be used to distinguish myocarditis from other diseases in the pediatric patient.
This observational study aimed to ascertain the number of patients with viral illness who have subclinical myocarditis using Troponin I (Tnl) as a diagnostic tool.
34 Skoune HK, Dec GW, Friedrich MG, Cooper LT. Noninvasive imaging in myocarditis. J Am Coll Cardiol 2006; 48:2085–2093.

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44 Klugman D, Berger JT, Sable CA, et al. Pediatric patients hospitalized with myocarditis: a multi-institutional analysis. Pediatr Cardiol 2009. [Epub ahead of print] This descriptive study aimed to assess hospital and patient level variables that could help predict myocarditis outcomes. Considerable variability was noted among the cases, resulting in an inability to predict outcome based on characteristics of the patient or level of severity on presentation.
48 Frobel AK, Hulpe-Wette M, Schmidt KG,Laer S. Beta-blockers for congestive heart failure in children. Cochrane Database Syst Rev 2009;CD007037. This Cochrane Review evaluated the outcomes of children with congestive heart failure who received beta-blockers as part of the treatment regimen. The result of this meta-analysis was that there continues to be a lack of evidence to support or discourage this form of therapeutic management in pediatric patients with CHF.