Challenges and Opportunities in Pediatric Heart Failure and Transplantation

Diagnosis and Treatment of Myocarditis in Children in the Current Era

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Myocarditis has been defined by the World Health Organization/International Society and Federation of Cardiology as an inflammatory disease of the heart muscle diagnosed by established histological, immunologic, and immunohistological criteria.[1] Insights into its clinical manifestation and treatment in both adults[2–7] and children[8–12] have been the subject of a number of recent reviews. It is caused primarily by numerous infectious agents, but it may also accompany autoimmune disease, hypersensitivity reactions, and toxins (Table 1). In North America and developed countries, it primarily has a viral origin. In Central and South America, *Trypanosoma cruzi* (Chagas disease) is a common cause. Diphtheria often causes myocarditis in countries without widespread immunization.[13] Although enteroviruses have classically been identified as the prime viral agent, new techniques to extract viral genome from myocardium with polymerase chain reaction techniques have in both children and adults revealed previously unrecognized viruses such as adenovirus, parvovirus B19, human herpesvirus 6, hepatitis C, Epstein-Barr virus, and cytomegalovirus.[2,3,14–19] Interestingly, the pattern of identified viral pathogens in myocarditis has evolved over the last 20 years from enteroviruses and adenoviruses to primarily parvovirus and herpesvirus 6. Endomyocardial fibroelastosis, a once frequent cause of infantile dilated cardiomyopathy that is now rarely seen, was linked to the mumps virus via viral polymerase chain reaction analysis of archived pathological sample, suggesting that its reduced prevalence might be attributed to immunization.[20]

In a somewhat confusing fashion, the American Heart Association's contemporary definitions of cardiomyopathies classify myocarditis as an inflammatory cardiomyopathy but also lists the same infectious causes of dilated cardiomyopathy as those found with myocarditis.[21] This conundrum typifies myocarditis. Its myriad presentations range from minimal symptoms to severe heart failure and sudden death. It is commonly associated with typical abnormalities observed in ECGs, cardiac imaging, and cardiac biomarkers, but it may exist in the absence of those abnormalities. It is a disease defined by observable myocardial pathology but may be present despite normal-appearing cardiac biopsies. Immunosuppression and immunomodulation have been used to treat myocarditis in children for >20 years, but their use remains controversial. These variations and controversies make the diagnosis and treatment of myocarditis in children a fascinating challenge and are the subject of this report.

Diagnosis

History and Physical Examination

Tachypnea and an abnormal respiratory examination were the most frequently described presenting symptoms in emergency department patients ultimately diagnosed with myocarditis.[22] Isolated gastrointestinal symptoms of anorexia, abdominal pain, and vomiting may also occur.[23,24] Chest pain, syncope, and palpitations may also be presenting complaints. Fever may or may not be present. The majority of patients present with a resting tachycardia, but other cardiac-specific signs such as pallor, hypotension, edema, and hepatomegaly occur in only a minority of cases. Often, multiple visits to medical personnel occur over time before a diagnosis is made.[25]

Electrocardiography

ECGs are virtually always abnormal in children with myocarditis, but a normal ECG does not rule out the possibility of the disease.[23] ECG abnormalities, however, are widely variable, and there is not one specific abnormality that occurs with enough frequency to be a specific marker. Low-voltage QRS complexes can exist. ST-T wave abnormalities to ST-segment elevation mimicking acute myocardial infarction may occur.[26,27] Atrial and ventricular delays and prolongation of QT intervals may also occur. Premature contractions and a wide variety of tachyarrhythmias and bradyarrhythmias occur in myocarditis, including complete atrioventricular block.[28,29]

Biomarkers

Nonspecific markers of inflammation (white blood cell count, C-reactive protein, and erythrocyte sedimentation rate) are often elevated in myocarditis, but normal studies do not exclude a myocardial inflammatory process.[5] Since the development of blood levels of cardiac troponin T and I as a marker of cardiomyocyte damage or death, elevations of these cardiac proteins in the blood are observed in a substantial minority, but not a majority, of adults and children with myocarditis.[30–32] Their absence does not rule out the presence

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Table 1. Various Causes of Myocarditis[3,5]

Causes	Examples
Infectious	Viral: adenoviruses, echoviruses, enteroviruses (eg, coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza A virus, parvovirus B19
	Bacterial: chlamydia, *Corynebacterium diphtheria*, legionella, *Mycobacterium tuberculosis*, mycoplasma, staphylococcus, streptococcus A, *Streptococcus pneumoniae*
	Fungal: actinomyces, aspergillus, candida, cryptococcus
	Helminthic: *Echinococcus granulosus*, *Trichinella spiralis*
	Protozoal: *Toxoplasma gondii*, *Trypanosoma cruzi*
	Rickettsial: *Coxiella burnetti*, *Rickettsia typhi*
	Spirochetal: *Borrelia burgdorferi*, leptospira, *Treponema pallidum*
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematodes, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitivity reactions	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab
Toxic	Ethanol
Others	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

of the disease. Some of the highest values of high-sensitivity troponin are observed in myocarditis patients.[33] One pediatric study[22] found elevation of serum aspartate aminotransferase commonly present in their myocarditis patients. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide can be elevated in myocarditis,[7] and elevated levels may aid in distinguishing a cardiac from a noncardiac reason for respiratory symptoms in children.[34] Cardiac protein autoantibodies are often found in the serum of adult myocarditis patients, but their role as a pathogenic agent remains uncertain.[35] In a small pediatric pilot study,[36] antibodies to cardiac myosin were found in myocarditis patients at the time of diagnosis and persisted in previously diagnosed patients both with and without myocardial recovery.

Assessment of Viral Infection

Although determining acute and convalescent viral serologies is the traditional way to diagnose viral infections, it is likely of limited, if any, use in the determining viral origin in myocarditis.[5] Many of the viruses associated with myocarditis are highly prevalent in the population, and the development of myocarditis may occur well after the acute viral phase of the disease has resolved. Although viral polymerase chain reaction testing on endomyocardial biopsy samples is a clinically available test, polymerase chain reaction assessment of virus from the respiratory tract and other sites has also been recommended in children.[37] A potentially cardiotoxic virus was indentified from urine, stool, or upper respiratory secretion in 22.3% of pediatric dilated cardiomyopathies at presentation in the Australian registry.[38] Evaluation of new-onset pediatric myocarditis patients in a small pilot study[39] of blood polymerase chain reaction samples at the time of presentation found the presence of enterovirus, adenovirus, parvovirus B19, or human herpesvirus 6 in 43% of the patients compared with only 4% of a pediatric control group receiving a same-day surgery elective procedure.

Echocardiography

Echocardiography remains the most common tool to assess left ventricular structure and function in pediatrics. Although the most common echocardiographic finding associated with myocarditis is a dilated cardiomyopathy phenotype of left ventricular dilatation and reduced ejection fraction, hypertrophic and restrictive phenotypes have been described in histologically proven myocarditis.[40] Segmental wall motion abnormalities mimicking an ischemic cardiomyopathy can be observed.[41] Pericardial effusions suggestive of myopericarditis may also be observed and help to make a diagnosis. Fulminant myocarditis, a distinct symptom complex from acute myocarditis with a good prognosis, has a characteristic echocardiographic phenotype in adults[42] and children[43] of reduced left ventricular ejection, normal left ventricular cavity size, and increased septal thickening. It predicts a better chance for ultimate normalization of cardiac function.

Cardiac Magnetic Resonance Imaging

Currently, cardiac MRI (cMRI) may be the most helpful imaging tool for the diagnosis of myocarditis. In addition to its ability to accurately assess left ventricular ejection, chamber size, and wall thickness, cMRI can localize tissue injury, including edema, hyperemia, and fibrosis.[44] Assessment of myocardial edema is performed with T2-weighted imaging.[45] Hyperemia may be assessed with the use of T1 sequences obtained within minutes after gadolinium injection (early enhancement), which are highly reproducible but not the most specific for the diagnosis of myocarditis.[44,46] Late gadolinium enhancement in the subepicardial or transmural areas suggests the presence of myocardial fibrosis associated with myocarditis compared with the subendocardial pattern associated with ischemia.[47] Enhancement is often regional as opposed to global. A recent consensus conference[44] determined that cMRI can be used optimally in the diagnosis of myocarditis if a combination of these 3 criteria is used (Lake Louise criteria; Table 2). If 2 or more of these criteria are positive, cMRI findings correlated with clinical histology with a diagnostic accuracy of 78%. cMRI may be more helpful in the diagnosis of acute myocarditis if performed within 14 days of the onset of symptoms.[48] Identification of associated pericardial effusions may enhance diagnostic certainty.[49] Recent refinements in T1[50] and T2[51] mapping techniques may improve cMRI assessment of myocardial findings in myocarditis.

Endomyocardial Biopsy

Pathological confirmation of myocardial inflammation continues to be required for a definitive diagnosis of myocarditis.[1] More than 25 years ago, a pathological definition of myocarditis was developed (the Dallas criteria), requiring

Table 2. Lake Louise Cardiac MRI Diagnostic Criteria for Suspected Myocarditis[43]

Cardiac MRI finding are consistent with myocardial inflammation if at least 2 of the following criteria are present
Regional or global myocardial signal intensity increase in T2-weighted images
Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
There is at least 1 focal lesion with nonischemic regional distribution in inversion-recovery prepared gadolinium-enhanced T1-weighted images (delayed enhancement)
Cardiac MRI study is consistent with myocyte injury or scar caused by myocardial inflammation if the third criterion is present
A repeat cardiac MRI study between 1 and 2 wk after the initial cardiac MRI study is recommended if
None of the criteria are present but onset of symptoms isvery recent and there is strong clinical evidence for myocardial inflammation
One of the criteria is present
The presence of left ventricular dysfunction or pericardial effusion provides additional supportive evidence for myocarditis

MRI indicates magnetic resonance imaging.

inflammatory cellular infiltrate with and without associated myocyte necrosis.[52] It has become apparent that the Dallas criteria are limited by a high interobserver variability in biopsy interpretation, the need for multiple samples, and the inability to detect noncellular inflammatory processes.[7,53] The patchy nature of myocarditis also contributes to sampling error. The Dallas criteria may also be limited in the detection of myocarditis from viruses such parvovirus B19 and human herpesvirus 6, in which the primary pathology resides in endothelial injury.[4] Over the past decade, immunohistochemistry techniques have improved the detection of inflammation in endomyocardial biopsies. Monoclonal antibodies to CD3 allow the detection and localization of T cells and macrophages, respectively. HLA antigen can used to detect HLA class II expression in antigen-presenting immune cells. The World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies has defined inflammation in an endomyocardial biopsy by immunohistochemical detection of focal and diffuse mononuclear infiltrates (T cells and macrophages) with >14 cells/mm^2, in addition to enhanced expression of HLA class II molecules.[1] A recent study[54] developed an assay of transcriptomic biomarkers from a single biopsy sample to diagnose myocarditis with a high degree of accuracy. These techniques, if confirmed, could substantially change diagnostic algorithms for the detection of myocarditis.

A combined AHA/American College of Cardiology/European Society of Cardiology statement[55] on the indications for endomyocardial biopsy does not support its routine clinical use for the diagnosis of myocarditis. Biopsy is recommended only in patients with new-onset heart failure (<2 weeks) with hemodynamic compromise with and without left ventricular dilatation; new-onset heart failure of 2 weeks' to 3 months' duration with a dilated left ventricle, ventricular arrhythmia, and high-grade atrioventricular block (Mobitz type II or third-degree atrioventricular block); or symptoms unresponsive to treatment in 1 to 2 weeks. The last 2 scenarios occur in giant cell myocarditis, a rare disorder that occurs primarily in adults but has been reported in children.[56] Giant cell myocarditis has a grim prognosis but if identified can respond to treatment with immunosuppression.[57]

Sagar et al[6] have proposed a 3-tier classification for the clinical diagnosis of myocarditis (Table 3). Definite myocarditis would require histological or immunohistological evidence of myocarditis. Possible subclinical acute myocarditis describes a clinical situation of possible myocardial injury without cardiovascular symptoms but with at least 1 of the following: increased levels of cardiac injury biomarkers, ECG findings of

Table 3. Diagnostic Classification for Patients With Myocarditis[6]

Criteria	Pathological Confirmation	ECG or Imaging
Possible subclinical acute myocarditis	Absent	Needed
In the clinical context of possible myocardial injury without cardiovascular symptoms but with at least 1 of the following		
Biomarkers of cardiac injury raised		
ECG findings suggestive of cardiac injury		
Abnormal cardiac function on echocardiogram or cardiac MRI		
Probable acute myocarditis	Absent	Needed
In the clinical context of possible myocardial injury with cardiovascular symptoms and at least 1 of the following:		
Biomarkers of cardiac injury raised		
ECG findings suggestive of cardiac injury		
Abnormal cardiac function on echocardiogram or cardiac MRI		
Definite myocarditis	Needed	Not needed
Histological or immunohistological		

MRI indicates magnetic resonance imaging.

cardiac injury, or abnormal cardiac function on echocardiogram or cMRI. Many cases of myocarditis are thought to be asymptomatic. Possible subclinical myocarditis would describe situations such as that observed in the influenza A epidemic (H3N2) in Japan from 1998 to 1999, in which myosin light chain was elevated in 11.4% of patients,[58] or when 0.5% of patients had increased troponin I levels without cardiac symptoms after smallpox vaccination.[59] Probable acute myocarditis would be diagnosed with the same conditions as possible subacute myocarditis plus the presence of cardiovascular symptoms.

Cardiovascular Syndromes Observed With Pediatric Myocarditis

Sudden Death

Sudden death in the pediatric population is commonly associated with myocarditis. Sudden death occurred in 57% of autopsied patients with a diagnosis of myocarditis at a single pediatric center[60] over 10 years at a median age of 10 months (range, 10 days–16 years). Studies of sudden infant death syndrome have linked infection with viruses such as enterovirus, adenovirus, parvovirus B19, and Epstein-Barr virus and myocarditis to sudden infant death syndrome victims.[61,62] Myocarditis accounted for ≈9% of sudden deaths in young athletes in the United States in whom a confirmed cardiovascular event was documented.[63]

Arrhythmias

Symptoms such as palpitations and syncope occur in pediatric myocarditis patients even in the absence of heart failure or demonstrable reduction of left ventricular function. Myocarditis should always be considered in a child with acquired complete heart block. Lyme carditis[64] and Chagas disease[65] have been associated with complete heart block. Although the majority of children may recover atrioventricular conduction,[29] most patients need implantation of a permanent pacemaker because recovery may take weeks to months. Pediatric ventricular arrhythmias in structurally normal hearts[66] and ventricular tachyarrhythmias in athletes have been associated with myocarditis.[67]

Chest Pain/Myocardial Infarction

More than 20 years ago, it was recognized in adults[68] and children[69] that myocarditis may mimic myocardial infarction with severe symptomatic chest pain, characteristic ECG findings, and elevation of serum creatinine kinase in the presence of normal coronary angiograms. Coronary spasm has been observed with this presentation in adults.[70] Parvovirus B19 has been found in the myocardium of such patients, as well as adenovirus and Epstein-Barr virus.[71] In a study of 4436 patients presenting to a pediatric emergency department with chest pain, 24 had a confirmed cardiac origin, of whom 4 were diagnosed with myocarditis.[72] A recent study[27] of pediatric patients presenting with myocarditis and a chest pain/myocardial infarction pattern found that all had elevations of cardiac troponin I (peak range, 6.54–64.59 ng/mL) in the presence of normal values of erythrocyte sedimentation rate and C-reactive protein. Echocardiograms demonstrated a mild reduction in left ventricular function in 57% of the patients, and 5 of 6 patients demonstrated cMRI findings consistent with myocarditis. The prognosis was good with resolution of cardiac abnormalities within a few weeks, similar to the adult experience.

Acute Heart Failure With a Dilated Cardiomyopathy Phenotype

The classic presentation of myocarditis is the development of symptoms of heart failure with a dilated cardiomyopathy phenotype a few weeks after a history compatible with viral illness, including fever, myalgias, and respiratory or gastrointestinal symptoms. Myocarditis accounts for 30% to 35% of children with dilated cardiomyopathy phenotypes in the Australian[73] and North American[74] pediatric cardiomyopathy registries and for 22% of new-onset left ventricular dysfunction in the United Kingdom.[75]

Fulminant myocarditis[76] is a distinct subset of acute myocarditis characterized by heart failure with severe hemodynamic compromise requiring inotropic or mechanical circulatory support and at least 2 of the following criteria: fever, distinct onset of heart failure symptoms within a 1- to 2-day period, and a history consistent with viral illness within the 2 weeks before hospitalization. Despite the severe presentation, outcomes are substantially better than in adults with acute myocarditis. Acute myocarditis presenting with severe heart failure, arrhythmias, and lack of responsiveness to supportive care after 1 to 2 weeks leads to concern for giant cell myocarditis, which can be diagnosed by biopsy and has a grim prognosis, although is responsive to immunosuppression.[55]

Myocarditis in children is associated with a high rate of congestive heart failure, hospitalization, intensive care unit stay, and use of inotropic support at the time of diagnosis compared with children with idiopathic dilated cardiomyopathy.[43] A recent study of hospitalized patients in the United States[77] found that nearly half of the patients required inotropic support, 37.5% required mechanical ventilation, and 7.4% required extracorporeal membrane oxygenator (ECMO) support. Fulminant myocarditis has been described in children with mortalities varying from 48.4% in Japan[24] to 9% in France.[78]

Acute myocarditis in children has been associated with a good prognosis with a good chance for ultimate recovery of left ventricular dysfunction.[12,74,77,79,80] Within the North American Pediatric Cardiomyopathy Registry (PCMR;[43] Figure 1), 372 myocarditis patients diagnosed by biopsy (n=119) or clinical criteria (n=253) were compared with 1123 patients diagnosed with idiopathic dilated cardiomyopathy. Outcomes were similar in the biopsy and clinically diagnosed myocarditis patients and substantially better than in children diagnosed with idiopathic dilated cardiomyopathy. These results are similar to an estimated 58% spontaneous recovery in acute adult myocarditis gleaned from an adult meta-analysis.[81]

Treatment

Activity Limitations

Animal models of myocarditis have shown an association with sustained aerobic exercise and increased mortality.[82] Given these findings and the known association of myocarditis with sudden death in young athletes,[63] current guidelines from the 2005 Bethesda Conference for activity with acute myocarditis

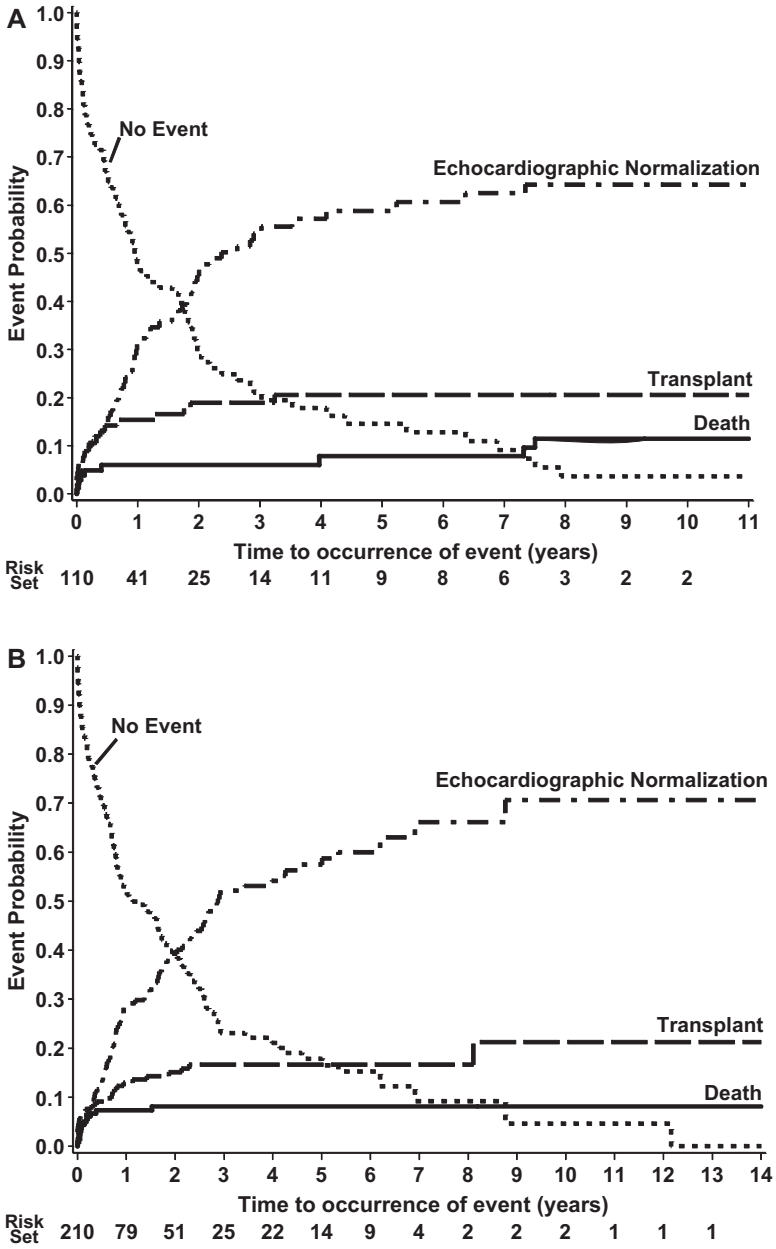

Figure 1. Competing outcomes analysis of crude incidence rates of echocardiographic normalization, cardiac transplantation, and death in patients diagnosed with myocarditis within the Pediatric Cardiomyopathy Registry.[43] **A**, Myocarditis diagnosed by endomyocardial biopsy. **B**, Myocarditis diagnosed clinically.

include exclusion from competitive athletics and other vigorous exercise for at least 6 months with a return to training and competition possible if left ventricular function is normal and there are no clinically relevant arrhythmias.[83]

Medical Therapy

Human studies on the use of conventional heart failure and arrhythmia therapy in myocarditis are lacking, but a number of animal studies have shown benefits to treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers,[84–86] aldosterone antagonists,[87] calcium channel blockers,[88] and carvedilol.[89] Metoprolol has been associated with increased mortality in acute murine coxsackievirus B3 myocarditis.[90] In adults, a recent study[91] showed that lack of β-blocker therapy was associated with a poor outcome. In adults, in recent-onset dilated cardiomyopathy in the Intervention in Myocarditis and Acute Cardiomyopathy II (IMAC-2) study,[92] routine use of angiotensin-converting enzyme inhibitors and β-blockers led to a transplantation-free survival of 88% and a survival free of heart failure hospitalization of 78%.

Digoxin is not recommended in the treatment of acute myocarditis[5] because animal studies have shown increased myocardial injury in virus-infected mice.[93] In a similar fashion, nonsteroidal anti-inflammatory drugs are also not recommended because of evidence of increased inflammation and mortality in murine models of myocarditis.[94,95]

Current recommendations in adult[2–6] and pediatric[9,10,12] myocarditis emphasize that supportive medical therapy should be the primary therapy for acute myocarditis. Treatment of heart failure and left ventricular dysfunction should proceed according to established guidelines of the AHA, American College of Cardiology, European Society of Cardiology, and Heart Failure Society of America.[96–98] These guidelines suggest

angiotensin-converting enzyme inhibition for asymptomatic left ventricular dysfunction (American College of Cardiology/AHA stage B heart failure), a combination of angiotensin-converting enzyme inhibition and β-blockade with selective use of aldosterone antagonists in symptomatic heart failure, and the use of inotropic agents with mechanical ventilatory or circulatory support for patients with cardiogenic shock or patients who deteriorate despite medical treatment. Because of the potential to treat giant cell or eosinophilic myocarditis with immunosuppression,[3–6,57] endomyocardial biopsy is recommended in this situation.[55]

Complete heart block is treated with pacemaker therapy, and therapy may be considered in second-degree block in entities such as giant cell myocarditis in which progressive block may occur.[57] Ventricular arrhythmias are treated by conventional guidelines.[99] Implantable defibrillators are implanted for symptomatic ventricular arrhythmias or previous cardiac arrest from ventricular fibrillation, but routine prophylactic implantation is often delayed in the hope that left ventricular function will improve with medical therapy.[5]

Immunomodulation, Immunosuppression, and Antiviral Therapy

Animal studies have suggested that myocarditis has a 3-phased course.[3,4,7,100] Phase 1 involves initial direct myocardial injury from the actively replicating virus or the innate immunological response from infection of cardiac myocytes, fibroblast, or endothelial cells. Phase 2 is marked by activation of antigen-specific immunity involving T cells, B cells, and antibody production. Various chemokines are present that may contain the inflammatory response but extend tissue injury. Development of autoantibodies and persistent T-cell activation can be induced by antigens intrinsic to the myocardium that cross-react with viral peptides (molecular mimicry). Ultimate outcomes may vary, as illustrated in Figure 2. Negative immune modulation may occur rapidly after elimination of the infectious pathogens, leading to a cessation of the inflammatory response with complete recovery or little long-term myocardial damage. However, phase 3 may occur in which acute myocarditis leads to a chronic dilated cardiomyopathy. This may result from severe myocardial injury caused by the acute event; an ongoing inflammatory, autoimmune process that may occur without the persistent presence of virus in the myocardium (inflammatory dilated cardiomyopathy); or ongoing direct injury from virus with or without a persistent myocardial inflammatory response (viral heart disease).[101]

These findings have suggested a role for both immunosuppressive and antiviral therapies in the treatment of myocarditis. Human studies have found biopsy evidence of cardiac inflammation in adults with idiopathic dilated cardiomyopathy[102,103]

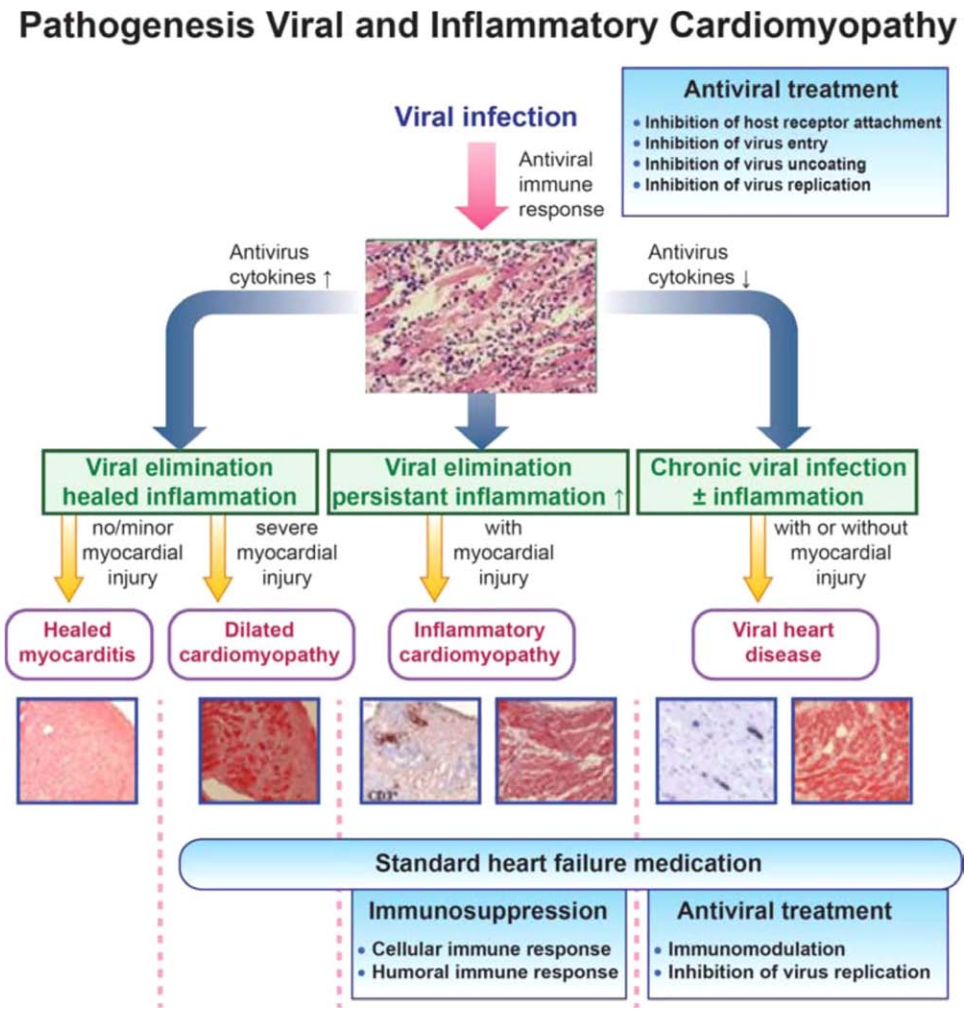

Figure 2. Proposed mechanism of how infection of cardiac endothelial cells or cardiac myocytes by virus leads to direct cellular damage. A subsequent innate and adaptive immune response develops that can evolve into resolution and healing or dilated cardiomyopathy resulting from severe initial injury, persistent inflammation, or persistent viral infection. Adapted from Schultheiss et al[4] with permission of the publisher. Copyright © 2011, Oxford.

and immunohistochemical evidence of myocardial inflammation in up to 40% of adults with a chronic dilated cardiomyopathy unresponsive to supportive care.[104] Viral genomes have been found in children[6] and adults[105] with idiopathic dilated cardiomyopathy, and 1 study found that viral persistence over time was associated with progressive cardiac dysfunction.[106] However, another study[91] found only persistent immunohistological signs of inflammation, not persistent positive histology or viral presence, to be predictive of poor outcomes. Other studies[107,108] have questioned whether the presence of virus in patients with chronic dilated cardiomyopathy has a functional or prognostic relevance and argue against a role for antiviral therapy.[109]

Antiviral therapy might have its greatest efficacy in the very early stages of myocarditis. Most patients with acute myocarditis are diagnosed weeks after viral infection, making it questionable whether the therapy could be given early enough to be beneficial. A small case study[110] demonstrated viral clearance, improvement in left ventricular size and function, and symptomatic improvement with the use of subcutaneous interferon-β in enteroviral and adenoviral myocarditis. A subsequent randomized, placebo-controlled phase II trial has been performed in adult virus + inflammatory dilated cardiomyopathy and by report[4,5,108,109,111] showed some clinical benefit but a diminished response in terms of viral clearance with parvovirus B19 and human herpesvirus 6 infections. This trial, however, has not been yet been published in full form.

On the basis of its known antiviral, anti-inflammatory, and immunomodulating effects[112] and a single-center study in pediatric myocarditis,[113] the use of intravenous immunoglobulin (IVIG) in recent-onset dilated cardiomyopathy was tested with a prospective, placebo-controlled trial (Intervention in Myocarditis and Acute Cardiomyopathy [IMAC]),[114] which showed similar high, not statistically significant rates of improvement in left ventricular ejection fraction in the IVIG and placebo groups. Unpublished experience[111] found benefit with cytomegalovirus hyperimmune globulin with cytomegalovirus myocarditis, and a recent study[115] found benefit of high-dose IVIG therapy in patients with idiopathic cardiomyopathy and high parvovirus B19 myocardial load. Immunoadsorption of anti-cardiac antibodies, although not clinically available universally, has been associated with improvement in left ventricular function in inflammatory cardiomyopathy in a single-center experience.[116]

Immunosuppressive therapy has a clear place in the management of giant cell[3,58] and eosinophilic[117] myocarditis. Generalization of its use to all forms of myocarditis remains controversial. More than 20 years ago, Parrillo et al[118] used prednisone to treat dilated cardiomyopathy, and the majority of patients with evidence of inflammation had a modest benefit in left ventricular ejection fraction (≥5%) and exercise tolerance. This trial was subsequently followed by a randomized, placebo-controlled trial in adults with histologically proven (with the Dallas[53] criteria) myocarditis[119] in whom immunosuppressive (prednisone with cyclosporine or azothioprine) treatment resulted in no change in left ventricular ejection fraction between groups at 6 months and no long-term difference in transplantation-free survival. Nearly half of the study subjects had relatively acute disease with <1-month duration of symptoms. Furthermore, left ventricular ejection fraction improved to a similar degree in the treatment and control groups.

Immunosuppressive therapy has been revisited recently, focusing on patients thought to have an inflammatory dilated cardiomyopathy characterized by symptoms that were unresponsive to time and conventional therapy for a number of months and myocardial inflammation defined by immunohistochemistry and histology.[1] Wojnicz et al[104] randomized patients with dilated cardiomyopathy with increased HLA antigen expression on biopsy to prednisone/azothioprine or placebo and found a significant improvement in left ventricular ejection fraction after 3 months of treatment. Frustaci et al[120] treated 41 patients with histological evidence of myocarditis and >6 months of symptoms with prednisone/azothioprine for 6 months and found that approximately half of these patients had improved left ventricular ejection fraction with 6 months of treatment. Compared with only 14% of the responders, 85% of the nonresponders had viral genome in the myocardium, and 90% of the responders had positive cardiac autoantibodies. These findings suggested that patients with evidence of inflammation and chronic (>6 months) symptoms without the presence of virus might be good candidates for immunosuppression. The subsequent randomized, placebo-controlled Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) trial[121] was done in patients with dilated cardiomyopathy fulfilling these criteria. Thirty-eight of 43 patients improved by the predefined end point of ≥10% improvement in left ventricular ejection fraction after 6 months of treatment and improvement in New York Heart Association class. The placebo-treated patients experienced a significant decline in left ventricular ejection fraction over the course of the study.

Concordant with the initial use of immunosuppression in adult myocarditis, a number of small case series, retrospective reviews, and mostly uncontrolled clinical trials[69,78,79,122–125] have been published on the use of various immunosuppression regimens in pediatric myocarditis. The regimens reported usually used steroids alone or in combination with azothioprine or cyclosporine. In aggregate, these regimens were studies in children at the time of their initial presentation and showed evidence of improvement in left ventricular function and excellent survival in 68% to 100% of cases. A review of these studies,[126] however, concluded that there was insufficient evidence to support the routine use of immunosuppression in pediatric myocarditis, citing problems with small sample size, lack of control groups, and variability in therapeutic regimens. A similar high rate of spontaneous improvement seen in adult acute myocarditis has also been observed in pediatric patients,[43,80] which makes interpretation of uncontrolled studies problematic. Burch[127] has suggested that these studies that demonstrated immunosuppression in acute pediatric myocarditis appeared to be safe but did not demonstrate that the prognosis of pediatric myocarditis was worse without immunosuppression.

Despite this controversy, prednisone is currently used in 25% to 30% of the cases of acute myocarditis in the United States,[43,128] although no effect on outcomes was observed with the use of steroids in the PCMR experience.[43] The use

of immunosuppression in children with more chronic inflammatory dilated cardiomyopathy has been poorly studied. One recent report[129] from Brazil studied the use of prednisone and azothioprine in 30 pediatric patients with an inflammatory dilated cardiomyopathy with symptoms of 5 months' to 11 years' duration, similar to the adult TIMIC study, but patients with the presence of viral genome in the myocardium also were treated. This study found improvements in treated patients regardless of the presence or absence of virus.

In 1990, Boston Children's Hospital and Children's Hospital of Los Angeles combined to include a 2-mg/kg dose of IVIG in the routine management of children presenting with presumed acute myocarditis on the basis of an observed improvement in left ventricular function after IVIG treatment in myocarditis associated with Kawasaki disease[130] and the effects of IVIG in a mouse model of enteroviral myocarditis.[131] Their experience in 21 consecutive children, published in 1994,[113] found that the use of IVIG resulted in significant improvements in left ventricular systolic function and nearly significant trends of decreased left ventricular dilatation and overall survival compared with a historical control cohort of 25 patients previously evaluated from 1985 to 1989. Aside from year of presentation, the IVIG group had a significantly greater number of patients treated with angiotensin-converting enzyme inhibitors (88%) compared with the control group (53%). Initial support in the IVIG group also included the significantly greater use of intravenous inotropes (90% versus 52%) and intravenous afterload (71% versus 20%) in the IVIG group compared with the historical controls. These differences suggest that a greater proportion of patients within the IVIG group may have had fulminant myocarditis.

Use of IVIG for the treatment of pediatric acute myocarditis has become widespread. In a study of pediatric acute myocarditis admissions in 42 American tertiary care hospitals from 2006 to 2011[128] (Figure 3), >70% of the patients received IVIG. A 2005 meta-analysis of the use of IVIG for acute myocarditis in children or adults[132,133] could not find enough evidence to recommend its routine use for acute myocarditis. Furthermore, a benefit of IVIG therapy cannot be discerned in recent single-center[80] and multicenter[43,77] outcome studies of pediatric myocarditis.

Therapy for Advanced Heart Failure/Cardiogenic Shock in Pediatric Myocarditis

Acute pediatric myocarditis is commonly associated with severe, progressive heart failure. The majority of patients receive care in an intensive care unit at presentation[43,128] and are treated with intravenous inotropes (Figure 3). Mechanical circulatory support is frequently required when pharmacological therapy is ineffective, as reflected in evidence of elevated blood lactate levels and evidence of end-organ dysfunction.[134] Most commonly, ECMO support is used. ECMO is currently used in ≈20% of American children hospitalized with myocarditis (Figure 3).[128] A number of single-center studies[134–137] have reported hospital discharge rates of ≈80% in pediatric myocarditis requiring ECMO support, with ≈60% of the patients experiencing myocardial recovery. Multicenter data from the Extracorporeal Life Support Organization (ELSO) registry demonstrated a lower hospital discharge rate of 61% in a 10-year period from 1995-2006.[138]

ECMO provides biventricular circulatory support but does not decompress the left ventricle. Patients placed on ECMO will initially demonstrate a stunned left ventricle with no effective ejection, which can lead to a need for decompression of the left ventricle via a left-sided vent or atrial septostomy in as many as 30% of cases[138] to avoid pulmonary venous hypertension and pulmonary hemorrhage. Evidence of improved left ventricular ejection usually appears less than a week after the initiation of ECMO. Although ECMO can provide effective short-term (<2 weeks) support, survival was <50% in myocarditis patients requiring >2 weeks of support in the ELSO registry. Factors associated with death on ECMO have included the presence of arrhythmia on support,[134] the need for dialysis,[138] and higher stages of end-organ hypoperfusion, as reflected in serum lactate, creatinine, and aspartate aminotransferase levels.[134] In 1 center's experience, the absence of virus in the myocardium or evidence of myocardial inflammation was associated with a greater chance for recovery.[139]

Ventricular assist devices (VADs) have revolutionized the care of adults with advanced heart failure.[140] VAD support, usually in the form of left ventricular assist devices as opposed to biventricular assist device support, is being increasingly[128] used in pediatric myocarditis (Figure 3). Continuous-flow VADs, used in adults, are limited to use in older children and

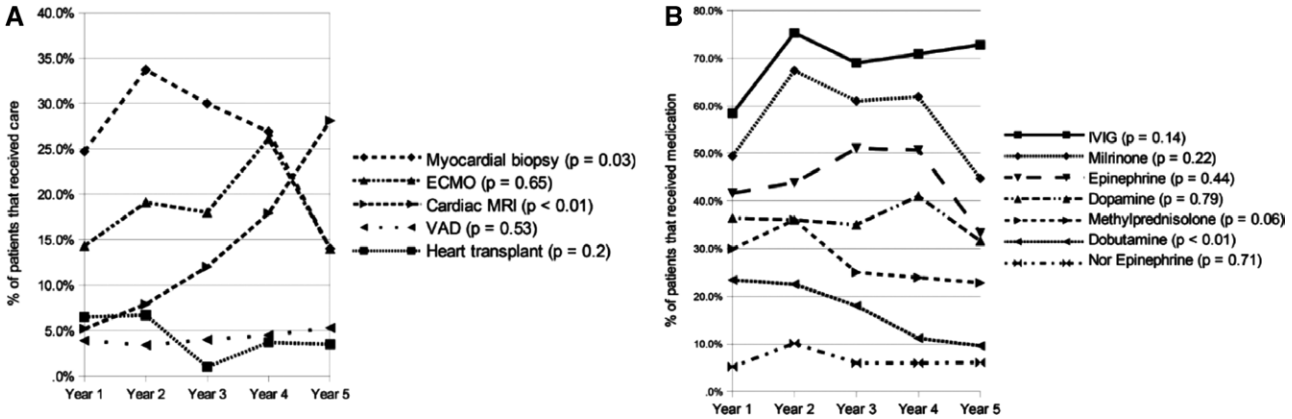

Figure 3. Temporal trends in use of diagnostic modalities and therapy in pediatric myocarditis in the United States.[129] ECMO indicates extracorporeal membrane oxygenator; IVIG, intravenous immunoglobulin; and VAD, ventricular assist device.

adolescents, although the Heartware device has been used in children as small as 0.8 m^2.[141] Initial experience with the use of these devices in the pediatric population is favorable, with low mortality and morbidity rates, similar to the adult experience.[142] Currently, the primary VAD used for support in children is the pulsatile Berlin Heart EXCOR, which comes in various sizes, allowing support for infants as small as 3.5 kg. Initial experience with the device in Germany was favorable,[143] and it has been available in North American for the last decade. Implantation of this device has occurred in >75 North American patients over the past 5 years,[144] and myocarditis represented 20% of the cardiomyopathy patients implanted with the device. US Food and Drug Administration approval was obtained for its use in 2011 after a US Food and Drug Administration–sanctioned trial demonstrated superior survival and safety compared with a propensity-matched cohort of patients supported with ECMO from the ELSO registry.[145]

The primary use of pediatric VADs is as a bridge to heart transplantation. In the Berlin EXCOR trial,[145] the mortality in patients on the device was 8%, and 87.5% of patients placed on the device received transplantations. This experience is similar to recent experience in pediatric patients using adult continuous-flow VADs.[142] The overall mortality rate in patients on device in the United States during the time period of the trial was 26% with a transplantation rate of 67%, reflecting the ability of centers to use the Berlin EXCOR on a compassionate-use basis during the conduct of the trial.[144] Lower patient weight (especially <5 kg), elevated serum bilirubin, lower estimated glomerular filtration rate, and use of biventricular assist device support were associated with mortality with the device.[144] These encouraging outcome results were tempered by high rates of neurological adverse events (29%, primarily thromboembolic stroke), major bleeding (44%), and major infection (44%).

The potential of VAD therapy to allow extended cardiac support has raised the hope that VADs could be used as a bridge to ultimate myocardial recovery and avoidance of transplantation. Although some series have found a VAD explantation owing to a recovery rate as high as 16%,[145] experience in the United States to date has been disappointing, with explantation rates of <10%.[143,144] However, within the overall worldwide pediatric Berlin EXCOR experience of >1200 implants (personal communication with Robert Kroslowitz, Berlin Heart, Inc; Figure 4), 24% of the patients implanted for myocarditis were able to be weaned from the device.

Although pediatric myocarditis is generally associated with improvement in and resolution of cardiac dysfunction, a substantial minority of patients (Figures 1 and 3) will have recalcitrant heart failure unresponsive to medical management that leads to heart transplantation. Outcomes for adult[146] and pediatric[147] heart transplantation have been reported to be similar to results for transplantation with other cardiomyopathies. Within the Pediatric Heart Transplant Study (PHTS) database, the 10-year survival rate after heart transplantation for dilated cardiomyopathy is ≈70%. Myocarditis accounted for 12% of the patients transplanted with a dilated cardiomyopathy phenotype within the PHTS. Recently, however, a subanalysis of PHTS data performed by a merger of the PCMR and PHTS databases (Figure 5) showed a 2.7-times increased risk of mortality in patients with myocarditis compared with other children with dilated cardiomyopathy.[148] Myocarditis patients were also older (median age, 11.4 versus 3.6 years) at the time of transplantation and were more likely to die of acute rejection (17% versus 3%) than other dilated cardiomyopathy patients within the PCMR.

Future Directions

It is already apparent[128] that cMRI will increase in importance as a tool for the diagnosis of pediatric myocarditis, and further refinements may enhance its diagnostic and prognostic abilities. The prognostic ability may also be improved by the assessment of multiple biomarkers of inflammation, neurohormonal activation, and fibrosis during the course of the disease. In addition, the recent[149,150] findings that genetic cardiomyopathies may express themselves in the context of other cardiac stressors such as the postpartum period suggest that viral infection might trigger the same phenomenon in children. These possibilities will begin to be explored in recently initiated genetic studies and blood biomarkers in pediatric myocarditis within the infrastructure of the PCMR study centers (NIH/NHLBI 1RO1HL111459-01, 1RO1HL109090-01A1).

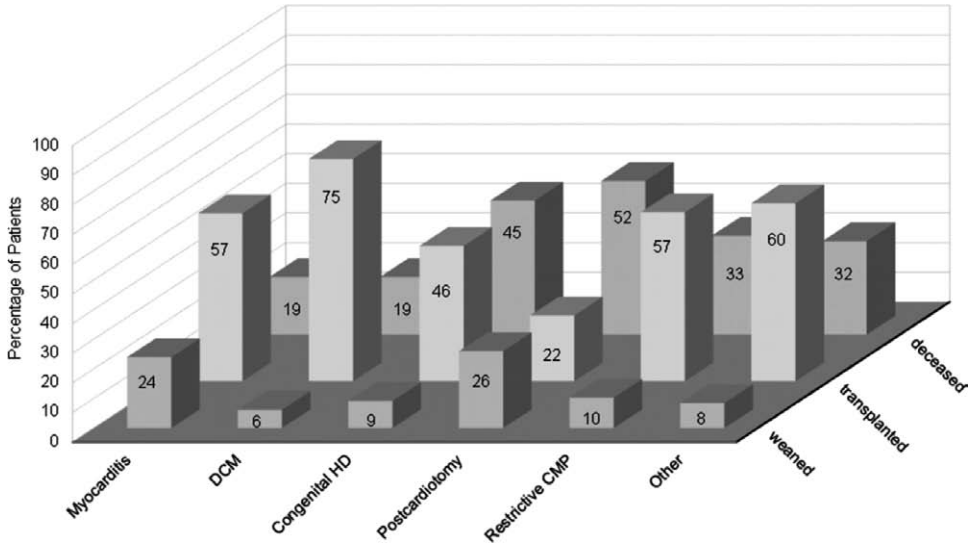

Figure 4. The proportion of pediatric patients within the Berlin Heart EXCOR database weaned, transplanted, or deceased for whom the indication for implantation was myocarditis, dilated cardiomyopathy (DCM), congenital heart disease (HD), postcardiotomy, restrictive cardiomyopathy (CMP), and other.

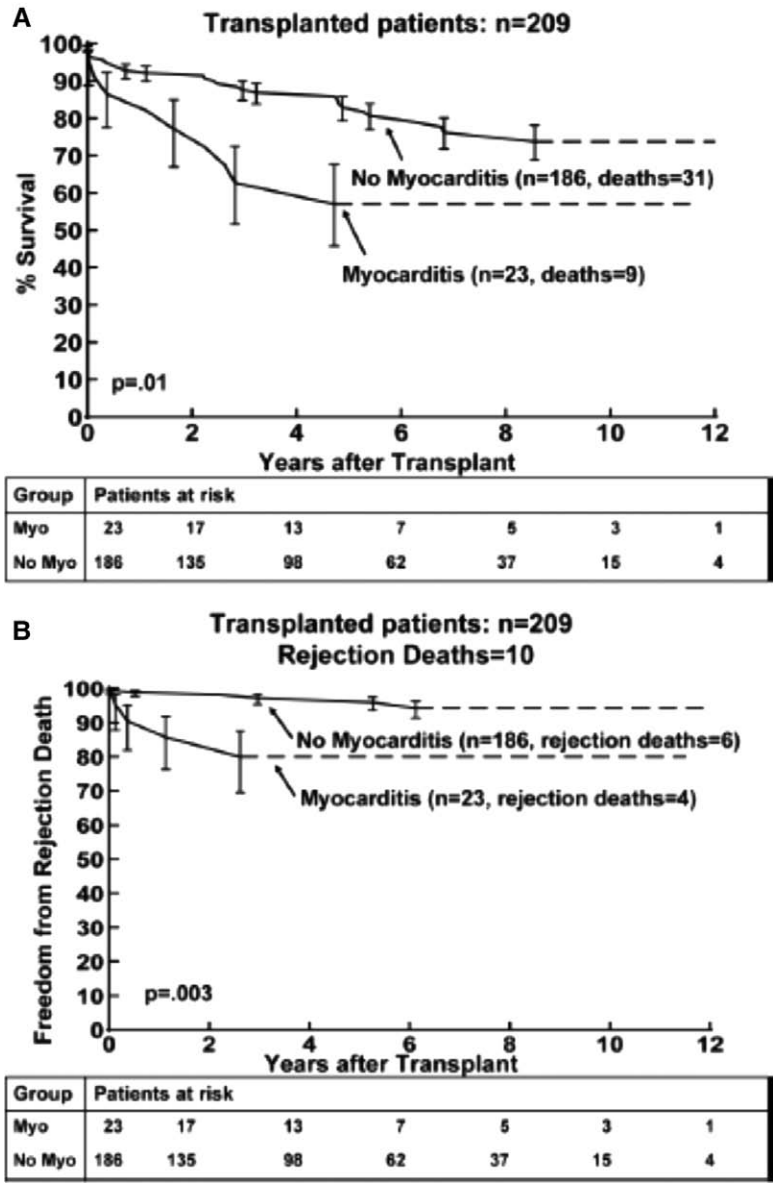

Figure 5. Kaplan-Meier posttransplantation survival curves for children in the merged Pediatric Cardiomyopathy Registry/Pediatric Heart Transplant Study diagnosed with myocarditis at presentation vs other patients with a dilated cardiomyopathy phenotype.[150] Error bars represent 70% confidence limits.

Most biopsy diagnoses of pediatric myocarditis have used the Dallas criteria.[38,43] Future application of the more recent histochemical criteria[1] in pediatric myocarditis could serve to identify the presence of inflammatory cardiomyopathy in children with chronic dilated cardiomyopathy. The small sample size and large rate of spontaneous recovery may preclude a definitive trial to determine the true benefit of immunomodulation/immunosuppression in acute pediatric myocarditis. However, dilated cardiomyopathy in children continues to carry an ominous prognosis, and transplantation remains the primary reason for improved survival in that disease.[151,152] The use of immunosuppression/immunomodulation in children identified with an inflammatory cardiomyopathy might further reduce the need for transplantation in children with a chronic dilated cardiomyopathy.

Miniaturization of continuous-flow, implantable VADs is currently undergoing development by private industry[139] and governmental support.[153] Human clinical trials will occur in the next few years. If these devices can provide a stable amount of cardiac support with low morbidity, as is evolving in the adult population,[154] they may offer the ability to provide long periods of support to increase the duration of the window of time for recovery from acute myocarditis for children of all ages and size, which could decrease the need for transplantation. The timing for the initiation of mechanical support needs to be further refined. Does, as some centers have hypothesized,[139] early left ventricular decompression with temporary VADs or followed, if needed, by durable VADs offer a better therapeutic strategy than ECMO or inotropic support?

Better assessment of long-term outcomes in pediatric myocarditis is likely warranted even in patients who have had apparent recovery. The essential difference between myocardial recovery and reverse remodeling has recently been emphasized.[154] If truly pediatric myocarditis is associated with complete recovery, study of these cured children may provide clues to the mechanism of myocardial recovery from heart failure that would benefit all patients with dilated cardiomyopathy regardless of age.

Disclosures

Dr Canter has received travel reimbursement from Berlin Heart, Inc. Dr Simpson reports no conflicts.

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