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Original Article

Outcomes for children with acute myocarditis

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Abstract The optimum treatment for myocarditis in children is unknown. We present outcomes for this disease as seen in a large series of children. Thus, we identified all children seen with myocarditis at Children's Hospital of Pittsburgh since 1985, including only those with biopsy-proven myocarditis, or cardiac dysfunction and proof of concomitant cardiotropic viral infection. Outcomes were defined as complete recovery, incomplete recovery, and death or transplantation.

We identified 41 patients, 37 proven by histology, and 4 patients who were too unstable for biopsy but had proof of viral infection. Of the group, 27 (66%) made a complete recovery, 4 (10%) had incomplete recovery, and 10 (24%) either died (5) or underwent transplantation (5). The median time to death or transplantation was 8.4 months, with a range from 1 day to 49 months. Steroids had been administered to 16 patients, of whom 10 made a complete recovery, 2 an incomplete recovery, 2 died, and 2 were transplanted. Intravenous immune globulin was given in isolation to one patient, who made a complete recovery, and to 18 in combination with steroids, of whom 12 made a complete recovery, 2 an incomplete recovery, 2 died, and 2 were transplanted. The remaining 6 patients received neither steroids nor intravenous immune globulin, and of these, 4 made a complete recovery, 1 was transplanted, and 1 died. Freedom from death or transplantation was 81% at 1 year, and 74% at 5 years, with no difference between the modes of treatments. The median time to recovery of function was also comparable between the groups. Thus, in our patients, treatment with intravenous immune globulin appeared to confer no advantage to steroid therapy alone. These data emphasise the need for randomised trials to assess the efficacy of current treatments, as well as that of new therapies.

Keywords: Myocarditis; immunosuppression; steroids; immune globulin

Acute myocarditis is an important cause of morbidity and mortality in children. Current regimes of treatment are based upon the presumed effectiveness of immunomodulation using steroids, intravenous immune globulin, or other immunosuppressive medications.[1–5] Clinical data regarding the comparative efficacy of these strategies, nonetheless, is lacking. We present data on a large series of children with acute myocarditis, focusing on presentation, therapies employed, and outcomes. Our aim is to compare final outcomes, and time to recovery of normal left ventricular systolic function, in those children treated with steroids alone, versus those treated with steroids and intravenous immune globulin.

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Methods

We made a complete search of the database of the Division of Pediatric Cardiology at Children's Hospital of Pittsburgh, identifying all patients carrying the diagnosis of myocarditis and/or cardiomyopathy seen since 1985, along with all patients in whom an endomyocardial biopsy was performed, regardless of the diagnosis. We endorse an aggressive approach to

performing endomyocardial biopsy in children with suspected myocarditis, thereby minimising the number of patients presenting with acute symptoms of heart failure who do not undergo biopsy. Patients were included if they had myocarditis or borderline myocarditis using the Dallas criterions.[6] To avoid exclusion of patients with strong clinical evidence of myocarditis, but who were too critically ill to undergo endomyocardial biopsy, we also included those with evidence of acute myocardial dysfunction, such as symptoms of congestive heart failure for <2 weeks, and proof of concomitant acute infection with a cardiotropic virus. Proof of acute viral infection included positive viral culture, rise in specific anti-viral titres, positive fluorescent antibody test, or positive polymerase chain reaction studies on cerebrospinal fluid or endomyocardial biopsy specimens.

Data obtained included basic demographic information, presenting characteristics including physical exam, chest x-rays, and electrocardiogram, initial catheterisation data, hospital course including disturbances of rhythm, immunomodulatory, anti-arrhythmic, anti-congestive, inotropic and after-load-reducing therapies employed, initial and serial echocardiographic data, and outcome. For analysis of left ventricular function, we used the shortening fraction as assessed from the parasternal short-axis view. Depressed left ventricular function was defined as a shortening fraction of less than 28%, or the requirement of inotropic support to maintain shortening fraction at the level of 28%, or the presence of focal abnormalities of wall motion with or without the use of inotropes. For comparative analyses, we divided patients into groups based upon the primary immunomodulatory therapy employed at diagnosis. One group received steroids alone, the second group received steroids together with intravenous immune globulin, the third group received intravenous immune globulin alone, and the fourth group received no immunomodulatory medications. Steroid doses ranged from 2 to 10 mg/kg/day for a minimum of 3 days, and the dose of intravenous immune globulin was 2 g/kg in all but 2 patients, each of whom received 1 g/kg. Survival analysis was undertaken using death or transplantation as final outcomes. Secondary outcomes analysed included time to recovery of normal left ventricular function, and incomplete recovery, the latter defined as survival with residual left ventricular systolic dysfunction.

Statistics

Basic demographic data was described using standard statistical methods. Kaplan-Meier survival curves were generated for all patients, and also for the patients receiving steroids alone, and those receiving steroids plus intravenous immune globulin. The group survival curves were compared using the log rank test with a p value of <0.05 considered significant. Time to recovery of normal left ventricular systolic function for patients receiving steroids alone, and for those receiving steroids plus intravenous immune globulin, was also assessed using a Kaplan-Meier survival curve. Risk factors for adverse outcome, which was defined as death or transplantation, and incomplete recovery, were defined through univariate analysis using the chi-square test.

Results

A total of 41 patients met the criterions for inclusion. Histologic evidence of myocarditis was present in 37 patients, including 35 endomyocardial biopsies, 1 autopsy examination, and 1 examination of the explanted heart. Left ventricular dysfunction of acute onset, with concomitant evidence of acute infection with a virus known to cause myocarditis, was found in 4 patients. No patient suffered a biopsy-related complication during the acute illness, and all biopsies were obtained via the internal jugular vein. General anaesthesia was employed when necessary. Six patients were referred to our center for possible mechanical ventricular support and/or cardiac transplantation. There were 21 males and 20 females, with 33 patients being Caucasian, 7 African American, and 1 Indian. Median age at diagnosis was 2.2 years, with a range from 5 days to 17.7 years.

General presenting characteristics and chief complaints are shown in Table 1. Specific features relating to cardiovascular involvement and instability at presentation are displayed in Table 2. Table 3 depicts clinical and demographic characteristics of patients receiving steroids alone, and of those receiving steroids and intravenous immune globulin. The groups are similar in all respects regarding clinical severity, but patients treated with intravenous immune globulin were significantly older at diagnosis.

An identifiable viral aetiology was found in one-third (Table 4). In the 4 patients for whom no biopsy

Table 1. General presentation characteristics and chief complaints.

Acute presentation (<2 weeks)	85%
Infectious prodrome	71%
Chief complaint	
Respiratory	56%
Weakness/decreased activity	17%
Chest pain	7%
Syncope	5%
Gastrointestinal	2%
Non-specific	10%
None	2%

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Table 2. Incidence of specific cardiovascular features at presentation.

Mechanical ventilation required	54%
Arrhythmias	
Ventricular tachycardia	8%
3rd degree AV block	13%
Pathologic Q waves	10%
Low voltage	63%
Non-specific ST-T wave changes	78%
Echocardiogram	
Decreased shortening fraction (<28%)	88%
Dilated left ventricle	45%
Catheterization*	
Elevated wedge (>12 mmHg)	65%
Decreased cardiac index (<2.5 l/min/m^2)	3%

*Catheterization data obtained after initiation of aggressive afterload reduction and inotropic support were initiated

Table 3. Clinical characteristics of patients treated with steroids alone and in those treated with steroids and intravenous immune globulin.

Variable	Steroids	Steroids + IVIG
Number	16	18
Gender (male:female)	9:7	8:10
Admit age, months (mean/median)	34/14	85.1/84.5
Cardiomegaly	11	13
Dilated left ventricle	9	7
Need for intubation	11	8
Need for inotropes	12	14
ICU admission	14	16
ICU LOS (mean/median)	13.7/9.5	13.9/10
LVAD/ECMO	4	2

Abbreviations: IVIG: intravenous immune globulin; ICU: intensive care unit; ICU LOS: intensive care unit length of stay in days; LVAD/ECMO: left ventricular assist device/extra-corporeal membrane oxygenation

Table 4. Viruses identified (1 patient had both Varicella and CMV infection).

Virus	Number	Source/Method
Coxsackie B	3	2 by rise in titre, 1 by positive culture from multiple sites
Adenovirus	3	Positive PCR from heart tissue
Cytomegalovirus	2	Positive FA antigen from nasopharyngeal swab and urine
Enterovirus	2	1 positive culture from CSF, 1 positive PCR from CSF
Influenza A	1	Positive culture from tracheal aspirate
Influenza B	1	Positive culture from tracheal aspirate and nasopharyngeal swab
Varicella	1	Strong clinical evidence
Picornavirus	1	Visual identification on electron micrograph

Table 5. Outcomes for patients diagnosed with acute myocarditis.

Outcome	All patients, n = 41	Excluding referrals*, n = 35
Complete recovery	27 (66%)	25 (71%)
Incomplete recovery	4 (10%)	2 (2%)
Deaths	5 (12%)	5 (14%)
Transplants	5 (12%)	3 (9%)

*Excludes 6 patients referred to our institution for transplant evaluation or for mechanical circulatory support

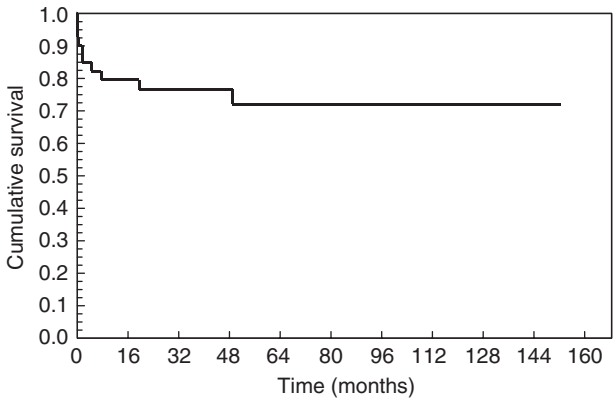

Figure 1.
Cumulative survival for all patients with myocarditis.

specimens were obtained, 1 had acute enteroviral infection diagnosed by polymerase chain reaction analysis of cerebrospinal fluid, 1 had influenza A positive culture from a nasopharyngeal aspirate, 1 had an acute rise in anti-Coxsackie B3 titres, and 1 had influenza B positive culture from a nasopharyngeal aspirate.

Four-fifths of patients required admission to the intensive care unit, with a median length of stay of 8 days, and a range from 1 to 57 days. Mechanical ventricular support was needed in 6 patients. The median length of hospitalisation was 13.5 days, with a range from 1 to 70 days. Symptoms of congestive heart failure in 8 patients resulted in readmission to hospital. A granulomatous myocarditis was seen on initial biopsy in one patient, who was subsequently readmitted for symptoms of congestive heart failure, and ultimately underwent cardiac transplantation after a period of mechanical ventricular support.

Overall survival was 75.6%. Individual outcomes are presented in Table 5, and cumulative survival for all patients is shown in Figure 1. For the entire group, median and mean time to adverse outcome was 1.5 and 8.4 months, with 4 patients dying or undergoing transplantation within 2 weeks of presentation. Survival curves for patients treated with steroids alone, and for those treated with steroids

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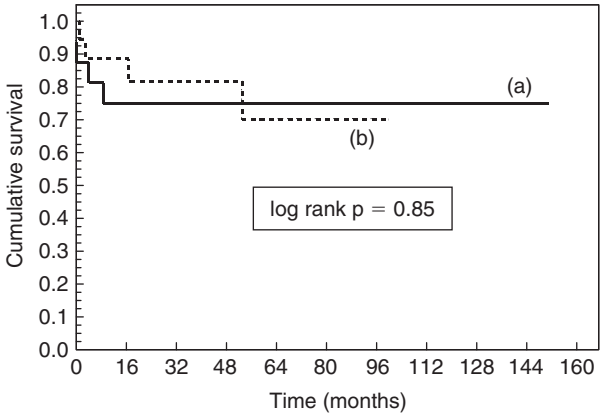

Figure 2.
Cumulative survival for patients with myocarditis treated with (a) steroids or (b) steroids + intravenous immune globulin.

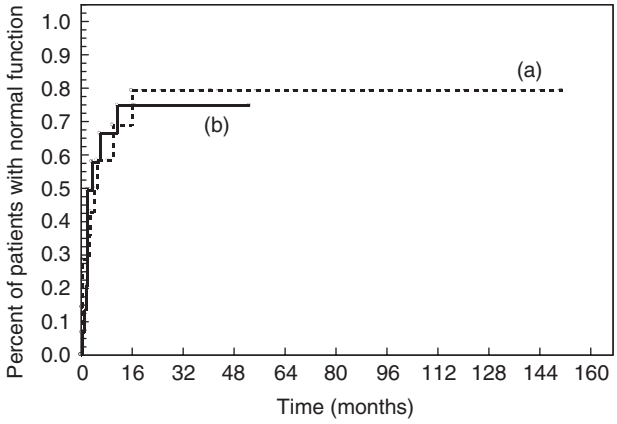

Figure 4.
Time to recovery of normal left ventricular systolic function for patients treated with (a) steroids or (b) steroids + intravenous immune globulin.

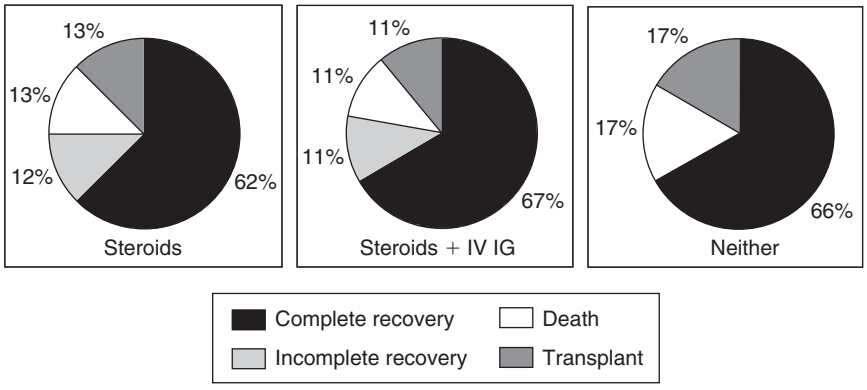

Figure 3.
Outcomes for patients treated with steroids, steroids + intravenous immune globulin, or neither.

and immune globulin, are presented in Figure 2. There was no difference in survival at all time points. Individual outcomes for patients treated with steroids, steroids plus intravenous immune globulin, and for those receiving neither steroids nor intravenous immune globulin, are shown in Figure 3.

Mean and median time to recovery of normal left ventricular function was 2.8 and 4.2 months in patients treated with steroids, and 2.0 and 3.2 months in patients treated with steroids and intravenous immune globulin. Recovery of normal left ventricular systolic function is shown in Figure 4. There was no difference between groups. Mean and median length of follow-up for patients treated with steroids was 60 and 38 months, and for patients treated with steroids and intravenous immune globulin was 34 and 28 months.

Risk factors for adverse outcome included the need for mechanical circulatory support, such as extra-corporeal membrane oxygenation or a left ventricular assist device, and readmission for symptoms of congestive heart failure after discharge following the initial course. The only risk factor identified for incomplete recovery was identification by the pathologist of extensive fibrosis on the initial biopsy.

Discussion

The use of immunosuppression for treatment of myocarditis probably began nearly 40 years ago.[7,8] Early clues regarding the role of activation of the immune system, and viral infection, in the pathogenesis of myocarditis came to light shortly thereafter.[9–12] Das went so far as to suggest the possibility of viral infection in, and subsequent alteration of, myocardial tissue, thereby making it immunogenic.[9] He suggested further elucidation of the roles of B and T cell function in cardiomyopathic states.

As the understanding of the pathophysiology of myocarditis progressed, debate regarding the use of steroids developed. Hirschman and Hammer[12] cited suggestions from Lerner[13] and Voight[14] that use of steroids be avoided during the acute phase of the illness, but employed later in the course of the disease.

The dichotomy between clinical and laboratory results on the use of steroids in myocarditis was

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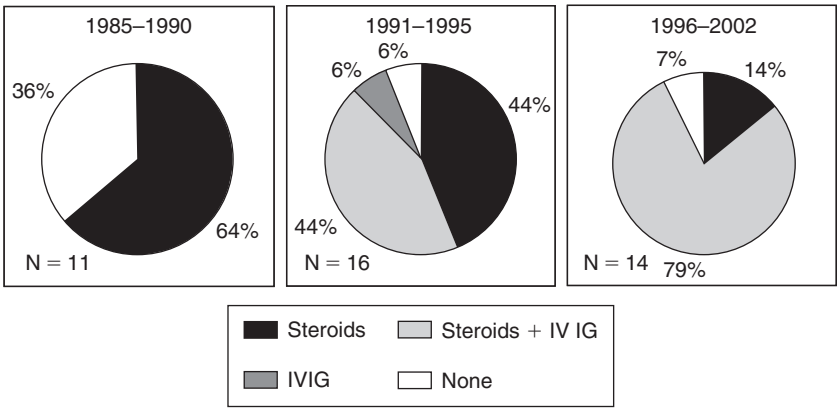

Figure 5.
Trend in choice of primary therapy for acute myocarditis at Children's Hospital of Pittsburgh.

highlighted in 1980 by Mason et al.[15] who suggested that endomyocardial biopsy should be undertaken to identify those patients with cardiac dysfunction of acute onset who have inflammatory myocardial infiltrates, thus making them candidates for immunosuppressive therapy. The arguments for[16] and against[17–19] the use of steroid immunosuppression continued into the 1990s.

The debate over the optimum treatment for acute myocarditis in children was intensified in 1994, with the assertion of Drucker et al. that the use of intravenous immune globulin was beneficial in acute myocarditis in terms of recovery of left ventricular function and survival.[1] This was supported in 1997,[20] but later evidence questioned the benefit of intravenous immune globulin.[21] The general trend seems to be toward the use of intravenous immune globulin, with or without steroids. This has been the case at our institution, as shown in Figure 5. Frequently cited as cause for avoiding the use of steroids in acute myocarditis is the possibility of exacerbating the disease through immunosuppression during the acute viremic phase, but the generalisability of animal studies in this area to our population of patients is questionable.

Probably the greatest challenge to successful management of acute myocarditis is prompt diagnosis, and clear assessment of the stage of disease. In our series, 4 patients suffered fulminant cardiovascular collapse and died or underwent transplantation within 2 weeks, 3 of whom were placed on mechanical circulatory support early in their course. The adverse outcome in these patients is unlikely to have been affected by the immunomodulatory regimen chosen, though one could argue that their prompt death resulted from steroid immunosuppression during the acute viremic phase, as all 3 received steroids initially.

We used strict criterions for inclusion of patients in our review. It is well known that many children presenting with cardiac dysfunction apparently of acute onset in reality have chronic cardiomyopathy.[22,23] The presentation of congestive heart failure in these patients may be precipitated by the stress of an acute illness, on an already marginal cardiovascular system. While the use of the so-called Dallas criterions has limitations, including sampling errors, variability in interpretation, and the possibility of missing cases in which florid myocardial viral invasion is occurring in the absence of a significant inflammatory response, there is no other current standard for diagnosing this disease. We feel that, at the present time, endomyocardial biopsy remains the best method for diagnosing acute myocarditis. Of course, the risk of endomyocardial biopsy can outweigh the benefits, especially in small children or in those for whom the diagnosis of myocarditis is likely based upon systolic dysfunction and concomitant proof of acute viral infection.

Clearly, there is no consensus regarding the optimum therapy for children with acute myocarditis, nor is there agreement about the role of endomyocardial biopsy in the diagnosis and management of this disease. Probably the most logical approach is that proposed by Liu et al.,[2] in which immunosuppression is avoided during the acute phase of the illness, but employed later, during the inflammatory activation. This approach makes endomyocardial biopsy all the more important, as it allows determination of the extent of the inflammatory infiltrate, and thus the likelihood of a positive response to immunosuppression.

The question of whether or not intravenous immune globulin confers a benefit to steroid therapy alone remains to be answered. Our data indicates that it does not. Retrospective analyses such as ours, nonetheless, have the obvious limitations of potential era effect, lack of randomization and blinding, and loss of follow-up. Studies assessing the relative efficacies of these therapies are needed, but unfortunately may not be possible. Given our incidence of 2.5 cases of biopsy-proven myocarditis per year in a population of 3 million patients, and an overall

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survival rate of approximately 75%, we estimate that it would take over 4 years of complete national enrolment to acquire the necessary number of patients in each group to show with adequate power a survival benefit of one therapy over another. With the obvious limitations to enrolment that such a study would entail, it would likely take more than 10 years to undertake such a trial. It may be that other measures of outcome, such as late death or transplantation, or residual ventricular dysfunction, or arrhythmias, would be more appropriate to assess the efficacy of these therapies.

In conclusion, we found that the addition of intravenous immune globulin to steroids when treating acute myocarditis provided no added benefit in terms of overall survival or time to recovery of normal left ventricular function. In addition, neither of these immunomodulatory approaches appears to confer a significant survival benefit over supportive care alone. Also, the outcomes for children with acute myocarditis have not changed significantly over the past 18 years at our institution, despite advances in the understanding of this disease, newer inotropic and afterload reducing-agents, and the introduction and refinement of mechanical ventricular support. The need for mechanical circulatory support or for readmission because of symptoms of congestive heart failure is a risk factor for death or cardiac transplantation, while extensive fibrosis seen on the initial biopsy predicts incomplete recovery of ventricular function.

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