RESEARCH

Treating Pediatric Myocarditis with High Dose Steroids and Immunoglobulin

Jenna Schauer[1] · David Newland[1] · Borah Hong[1] · Erin Albers[1] · Joshua Friedland-Little[1] · Mariska Kemna[1] · Thor Wagner[1] · Yuk Law[1]

Abstract
There is considerable variability in practice among pediatric centers for treatment of myocarditis. We report outcomes using high dose steroids in conjunction with IVIG. This is a single center retrospective study of children < 21 years of age diagnosed with myocarditis and treated with high dose steroids and IVIG from January 2004-April 2021. Diagnostic criteria for myocarditis included positive endomyocardial biopsy, cardiac magnetic resonance (CMR) imaging meeting Lake Louise criteria, or strictly defined clinical diagnosis. Forty patients met inclusion criteria. Median age at diagnosis was 11.6 years (0.7–14.6). Diagnosis was made clinically in 70% of cases ($N = 28$), by CMR in 12.5% ($N = 5$) and by biopsy in 17.5% ($N = 7$). Median ejection fraction (EF) at diagnosis was 35% (IQR 24–48). Median duration of IV steroids was 7 days (IQR 4–12) followed by an oral taper. Median cumulative dose of IV immunoglobulin (IVIG) was 2 g/kg. There were no serious secondary bacterial infections after steroid initiation. Ten patients (25%) required mechanical circulatory support. Overall transplant free survival was 92.5% with median follow-up of 1 year (IQR 0–6 years). Six patients required re-admission for cardiovascular reasons. By 3 months from diagnosis, 70% of patients regained normal left ventricular function. High dose steroids in conjunction with IVIG to treat acute myocarditis can be safe without significant infections or long-term side effects. Our cohort had excellent recovery of ventricular function and survival without transplant. Prospective comparison of a combination of high dose steroids with IVIG versus other therapies is needed.

Keywords Myocarditis · Intravenous Immunoglobulin · Steroid · Cardiomyopathy · Inflammatory heart disease · Pediatric heart failure

Introduction

Myocarditis is an inflammatory disease of the heart that is associated with significant morbidity and mortality. There is substantial variation in patient presentation ranging from subclinical or non-specific symptoms to acute heart failure or even sudden cardiac death.

The diagnosis of myocarditis can be challenging, especially in small children. In the modern era, use of the "gold" standard, endomyocardial biopsy, has been decreasing given the risks associated with invasive procedures and limited sampling of the myocardium [1, 2]. Cardiac magnetic resonance (CMR) imaging is gaining favor as it is non-invasive and can detect changes across the entire myocardium [3]. However, CMR is not universally performed to diagnose myocarditis in children due to limited availability, need for sedation, diagnostic criteria in children, and cost. Additionally, CMR has its own limitations with centers utilizing different imaging protocols and the possibility of ambiguous findings despite established CMR myocarditis criteria [4]. In the real world, most pediatric myocarditis diagnoses are based on clinical presentation, incorporating echocardiography, electrocardiography and cardiac specific biomarkers [5–7]—an approach supported by guidelines for the diagnosis of myocarditis in adults [9].

Best practice for treating myocarditis also remains controversial. Intravenous Immunoglobulin (IVIG) and steroids are both anti-inflammatory treatments commonly used though data supporting their benefits is limited and largely comes from adult studies [5, 9]. IVIG and steroids are frequently used in other inflammatory diseases in children such as

✉ Jenna Schauer
Jenna.Schauer@seattlechildrens.org

1 Seattle Children's Hospital, Seattle, WA, USA

Table 1 Diagnostic criteria

Endomyocardial Biopsy	Inflammatory cell infiltrate with or without myocyte injury
	Immunohistochemistry detection of inflammation, lymphocytes, myocyte injury, e.g. lymphocytes, anti-CD68, macrophages, HLA-DR upregulation, etc
	Positive tissue viral PCR for an agent previously reported to be associated with myocarditis
	Other features interpreted to be consistent with myocarditis of any etiology by the pathologist
CMR	Increased T2 signal intensity consistent with edema
	Increased early myocardial contrast enhancement relative to skeletal muscle consistent with hyperemia in gadolinium enhanced T1 weighted images
	Presence of late gadolinium enhancement (LGE) in T1 weighted images consistent with necrosis or scar
Clinical Diagnosis	Left Ventricular (LV) Dysfunction (EF < 55%, FS < 28%) OR focal LV dyskinesis with Left ventricular end-diastolic dimension (LVEDD) z score < + 3 without other explanation AND support from at least one of the below
	-Troponin > upper limits of normal
	-Presence of chest pain, pericardial effusion, EKG changes such as definitive (pathologic) diffuse ST elevation, PR depression or signs of ischemia
	-History, signs and symptoms of acute heart failure including cardiogenic shock or rapid progression upon admission
	-Positive respiratory virus polymerase chain reaction (PCR)/antigen test from respiratory tract swab where rest of the clinical scenario was consistent with presumed myocarditis
	OR Left Ventricular (LV) Dysfunction (EF < 55%, FS < 28%) OR focal LV dyskinesis AND positive blood viral PCR for well described etiologies of pediatric myocarditis (Cytelomegalovirus, Epstein-Bar Virus, Adenovirus, Enterovirus, Parvovirus, Human Herpes Virus 6, Human Herpes Virus 8, Herpes Simplex Virus)

Kawasaki Disease [10] as well as for treatment of rejection after cardiac transplantation. Given notable similarities between acute myocarditis and acute cardiac allograft rejection [11], our center has adopted a protocol using high dose steroids to treat myocarditis, modeled after our rejection treatment protocol. There is, however, concern of propagating direct viral injury to the myocardium when using steroids [6].

We examine our experience using high-dose steroids in combination with IVIG for the treatment of acute pediatric myocarditis.

Materials and Methods

Data Collection and Study Cohort

This is a single center retrospective study of children less than 21 years of age diagnosed with myocarditis from January 2004-April 2021 at Seattle Children's Hospital. Institutional review board approval was obtained prior to data collection. Study data were collected and uploaded into a secure Research Electronic Data Capture (REDCap©) database hosted at University of Washington [12, 13].

Patients were included in the study cohort if they met strict diagnostic criteria for myocarditis, which included one or more of the following: positive endomyocardial biopsy or positive CMR based on established Lake Louise Criteria [4] in the presence of left ventricular systolic dysfunction or focal left ventricular dyskinesis or echocardiographic criteria plus at least one clinical feature of myocarditis (Table 1).

Exclusion criteria included history of heart transplant, hemodynamically significant congenital heart disease,

Table 2 Reason for patient exclusion

Reason for exclusion	N
Received cardiotoxic medication	5
Hemodynamically significant congenital heart disease	3
Details of admission not available	6
Did not receive steroids	14
LVEDD Z score > 3	8
Met diagnostic Criteria for Kawasaki Shock	6
Myopericarditis or Pericarditis without LV dysfunction	15
Underlying rheumatic disease	3
Troponin leak due to vigorous activity	2
Underlying genetic/metabolic disorder (muscular dystrophy or mucopolysaccharide storage disease)	7
Shock secondary to another condition	3

cardiotoxic medications such as chemotherapy or an underlying systemic, genetic, or metabolic disorder or later diagnosis of a familial genetic basis for their disease. Patients who did not receive high dose steroids or IVIG, or had incomplete medical records were also excluded. Details of excluded patients can be seen in Table 2.

Demographic and clinical data were obtained from review of patient medical records up to 5 years after initial presentation. Data collected included basic demographic information as well as clinical information from admission and in follow-up. Outcome measures included overall and intensive care lengths of stay, need for mechanical circulatory support, heart transplant listing, heart transplant or death. Follow up data included serial echocardiographic measurements as well as heart failure medications upon discharge and at follow up.

Table 3 Steroid taper

Treatment day	Dose (methyl-prednisolone equivalent dose)
Days 1–3	10 mg/kg daily (maximum 750 mg)
Days 4–7	2 mg/kg daily
Week 2	1 mg/kg daily
Week 3	0.8 mg/kg daily
Week 4	0.7 mg/kg daily
Week 5	0.6 mg/kg daily
Week 6	0.5 mg/kg daily
Week 7	0.4 mg/kg daily
Week 8	0.3 mg/kg daily
Week 9	0.2 mg/kg daily
Week 10	0.1 mg/kg daily
Week 11	0.05 mg/kg daily

Table 4 Demographics

Demographics ($N=40$)	N (%) or median (IQR)
Gender	
Male	24 (60%)
Female	16 (40%)
Age at admission	11.6 years (IQR 0.7–14.6)
Weight	41.4 kg (IQR 8.8–78.6)
Height	142.1 cm (IQR 72.8–168.0)
BSA	1.28 m^2 (IQR 0.42–1.89)
Race	
American Indian or Alaska Native	2 (5%)
Asian	2 (5%)
Black	6 (15%)
Native Hawaiian or other Pacific Islander	1 (2.5%)
Other	7 (17.5%)
Unknown	2 (5%)
White	20 (50%)

Patients with myocarditis are managed or consulted on by the Heart Failure, Transplant, and Mechanical Circulatory Support (HF/TXP/MCS) service. Our standard myocarditis treatment protocol includes 2 g/kg IVIG based on actual body weight given over 48 h and an initial high dose steroid "pulse" that is tapered over 10–12 weeks. The details of the taper can be found in Table 3.

The initial 10 mg/kg steroid burst is typically given intravenously, with subsequent transition to enteral administration generally by day 7. Steroid regimens may be modified for certain patients due to concern for concomitant infection, concern for worsening of co-morbid conditions such as hypertension or hyperglycemia requiring insulin, or intolerance of side effects. Initiation of this steroid protocol can be delayed if there is concern for active systemic infection and pending diagnostic testing that will impact decision making. Patients were also included in the steroid cohort if they had acute myocarditis and received high dose steroids for alternate indications such as airway edema. In these cases, and to quantify oral steroids received, all dosing was converted to equivalent steroid potency doses. The ratio for equivalent glucocorticoid efficacy dosing is as follows: 0.75 mg dexamethasone: 20 mg hydrocortisone: 4 mg methylprednisolone: 5 mg prednisone: 5 mg prednisolone [14, 15].

Statistical Analysis

Descriptive statistics were performed. Data were reported as mean values and standard deviations or median values and interquartile ranges for continuous variables, and as frequency and percentages for categorical variables. Additionally, Kaplan-Meier curves were utilized to examine events over time. Data analysis was performed using SPSS 27 (SPSS Inc., Chicago, IL).

Results

Demographics

An initial medical record query for the diagnosis of myocarditis revealed 112 patients. Forty patients ultimately met inclusion criteria. The remaining 72 patients were excluded based on criteria detailed in Table 2. The study cohort had a median age of 11.6 years (IQR 0.7–14.6). The majority (60%) were male. Demographic details are outlined in Table 4.

Diagnostic Criteria

All patients met the above clinical criteria for myocarditis. The majority of patients were diagnosed based on clinical criteria alone ($N=28$, 70%). Seven patients had biopsy positive myocarditis. Biopsy findings consistent with myocarditis included evidence of inflammation ($N=7$, 100%), myocyte injury/necrosis ($N=5$, 71%), and edema ($N=5$, 71%); 3 patients (43%) also showed fibrosis. Five patients had CMR findings consistent with myocarditis. All positive CMRs met Lake Louise Criteria and showed significant areas of delayed gadolinium enhancement, LV dysfunction or regional wall abnormalities and were deemed consistent with myocarditis by the reading radiologist. An additional 2 patients who underwent biopsies and 4 patients who had CMR without

Table 5 Steroid equipotent doses received

Treatment day	Equipotent steroid dosing mg/kg/day [median(IQR)]
1	9.74 (6.78–10.02)
2	9.69 (7.87–10.00)
3	9.74 (5.74–10.04)
4	2.69 (1.82–5.00)
5	2.08 (1.73–4.92)
6	2.00 (1.27–4.91)
7	1.95 (1.09–4.00)

findings of myocarditis were included in the study because they met clinical criteria for myocarditis.

Baseline Echocardiographic Data

The initial echocardiogram showed severe LV systolic dysfunction (EF < 35%) in 21 patients (54%), moderate LV systolic dysfunction (EF 35–44%) in 6 patients (15%), and mild LV systolic dysfunction (EF 45–55%) in 4 patients (10%). Eight patients (21%) had a normal ejection fraction but with significant left ventricular dyskinesis or hypokinesis on echocardiogram. Median initial LV end-diastolic dimension z score was 0.02 (IQR − 0.87 to 1.79).

Twenty-two patients (65%) had at least mild mitral valve regurgitation, and 21 patients (53%) had at least mild tricuspid valve regurgitation on initial echocardiogram. Nine patients (23%) had at least a mild pericardial effusion.

Inpatient and Discharge Medications

Treatment with high dose steroids was initiated within 48 h of admission for 65.8% of patients. The median start time was on hospital day 2 (IQR 1–4, range 0–10). Thirty-eight patients (95%) received the initial pulse via intravenous (IV) route while 2 patients received their entire course enterally. The enteral courses were modified courses due to concern for potential infection. The median duration of IV steroid was 7 days (IQR 4–12). The median total duration of steroids received (IV and enteral) was 70 days (IQR 56–84). Steroid equipotent doses by day for the first 7 days are detailed in Table 5.

All patients received acid suppressive medication while receiving their steroid course. Intravenous Immunoglobulin (IVIG) was received by all patients. The average total dose of IVIG received was 2 g/kg (SD 1).

Thirty-two (80%) patients required inotropic support, the majority of which received milrinone (N = 29, 72.5%).

Twenty-five patients (62.5%) required 2 or more inotropes. Median inotrope duration was 11.5 days (IQR 5–17).

Thirty-eight patients (95%) received conventional heart failure therapy (including angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), digoxin, beta blockers or isosorbide dinitrate/hydralazine) during their inpatient stay. Similarly, 95% (N = 36) of patients were discharged on a regimen containing conventional heart failure medications.

Microbiologic Evaluation

Thirty-nine patients had viral PCR from the blood performed. Thirty-three patients had respiratory viral testing. Of these, seventeen patients were identified as having a specific viral diagnosis.

Twelve patients were found to have positive blood PCRs (6 enterovirus, 2 parvovirus, 1 mycoplasma, 3 human herpes virus-6). Of these patients, 9 had serial measurements. There were no increases in viral load after initiation of steroid pulse. All patients with serial measurements had resolution of viremia or bacteremia prior to discharge.

Nine patients were found to have positive respiratory viral panels (3 rhinovirus/enterovirus, 2 influenza B, 1 respiratory syncytial virus, 1 coronavirus OC43, 1 coronavirus 6NL3, 1 coronavirus HKU1, 1 influenza subtype 2009 H1N1). One patient was positive for both respiratory syncytial virus (RSV) and influenza B on viral respiratory panel as well as parvovirus on blood PCR. Another patient was positive for coronavirus 6NL3 tested positive for parvovirus as well on blood PCR. Two patients with positive viral testing for rhino/enterovirus were found to have positive blood PCRs for enterovirus.

Six patients had endomyocardial tissue PCR testing. All had negative tissue viral PCR. One patient had initial positive blood PCR for parvovirus but had no evidence of parvovirus on tissue sampling. This patient was readmitted 2 months after discharge with recurrent myocarditis and repeat endomyocardial biopsy was positive for parvovirus. No further biopsies demonstrated positive viral studies.

Outcomes

Of the cohort, 10 (25%) required mechanical circulatory support (MCS) during their initial hospitalization with extracorporeal membrane oxygenation (ECMO) being the most common form (n = 6; median 11 days, range 4–25 days). Three patients were supported with a left ventricular assist device (LVAD): 1 Centrimag (8 days), 1 HeartWare (149 days), and

1 Impella (3 days). One patient received biventricular support with Centrimags for 8 days. All patients underwent discontinuation of MCS, 9 (90%) due to clinical improvement and 1 LVAD (10%) was explanted due to complications with bleeding. The explant went well. No patients who required MCS died while on support or during admission. All but one patient was cannulated onto MCS prior to initiation of steroids. The remaining patient was cannulated within 12 h of steroid initiation. One patient who had been on ECMO died after discharge, and details of his death are delineated below.

Median overall length of stay was 15.5 days (IQR 8–28). Thirty-five patients (87.5%) required admission to the intensive care unit, with a median ICU length of stay of 12 days (IQR 7–27 days). Nineteen patients (47.5%) required intubation with mechanical ventilation for a median duration of 7 days (IQR 6–12 days).

Three patients (7.5%) either died or required transplantation. Two of these were listed for transplant during their initial hospitalization. The first patient was a 2-month-old with enterovirus myocarditis who required ECMO support for approximately 3 weeks. Despite successful decannulation, the patient had persistent heart failure and required a heart transplant prior to hospital discharge. The second patient was a 12-year-old with clinically diagnosed myocarditis. The patient showed no signs of myocardial recovery with medical therapy and died while on the waiting list during the initial hospitalization. He was not a VAD candidate due to significant obesity (BMI 50). No patients were listed or transplanted after discharge.

The third patient died unexpectedly 1.5 years after discharge. This patient required ECMO support at the time of initial presentation but was successfully decannulated and discharged with full recovery of ventricular function (most recent echo performed 5 months prior to death). Three weeks prior to death, the patient was diagnosed with RSV and recovered. One day before death, the patient developed vomiting and diarrhea and had a suspected aspiration event. The next day, the patient presented to the emergency room in extremis and could not be resuscitated. Autopsy showed evidence of aspiration pneumonia, histologic evidence of past myocardial injury, as well as evidence of infarction (without coronary artery disease) that may have occurred within 24 h of death. There was no evidence of recurrent myocarditis.

Three patients (7.5%) had sepsis during their hospitalization defined as hemodynamic instability in the setting of suspected infection with positive blood cultures. Admission blood cultures had been negative. Additionally, 1 patient had a soft tissue infection. There was no worsening of infection attributed to the use of steroids. Four patients had an atrial arrhythmia, 9 patients had a ventricular arrhythmia and 2 patients had cardiac arrest. Details of complications from

Table 6 Complications during hospitalization

Complication	Number of patients	Per-cent of patients
Infectious concern (pneumonia, sepsis, soft tissue infection)	5	12.5
Renal failure	5	12.5
Atrial arrhythmia	4	10
Ventricular arrhythmia	9	22.5
Cardiac arrest	2	5
Respiratory arrest	1	2.5
Neurologic event	5	12.5

myocarditis during the hospital stay can be found in Table 6. Fifteen patients (37.5%) were free from any of the below complications.

Definitions of complications .

(1) Pneumonia: new chest x ray infiltrate, received antibiotics
(2) Sepsis/Bacteremia: hemodynamic instability with positive microbiological cultures
(3) Thromboembolism
(4) Chronic renal failure: Required dialysis or renal replacement therapy

Six patients (15%) had readmissions for cardiac reasons: 3 with recurrent myocarditis, 1 with pericarditis, 1 with VAD dysfunction, 1 with hypotension. Timing of readmission ranged from 2 months to 2 years after the initial diagnosis.

There was no statistical significance on independent samples t-test between those with and without positive viral testing with regards to need for mechanical circulatory support, ICU length of stay, overall length of stay, sepsis, transplant listing, readmission or death.

Follow up Echocardiographic Data

Patients were censored from follow up at time of death, transplant or loss to follow up. The majority of patients showed improvement in left ventricular function over time with 42% (13 out of 31) showing normalization of ejection fraction by 1 week, 65% (22 out of 34) by 1 month, and 70% (14 out of 21) by 1 year. Figure 1 shows normalization of EF and regional wall motion abnormalities over time. Median LVEDD Z score remained the same or decreased (Fig. 2), and LVESD z score similarly decreased showing normalization over time. Of note, the 2 patients with initial LVEDD > 3 were those with definitive diagnosis by biopsy or positive serum PCR. Both of these patients had
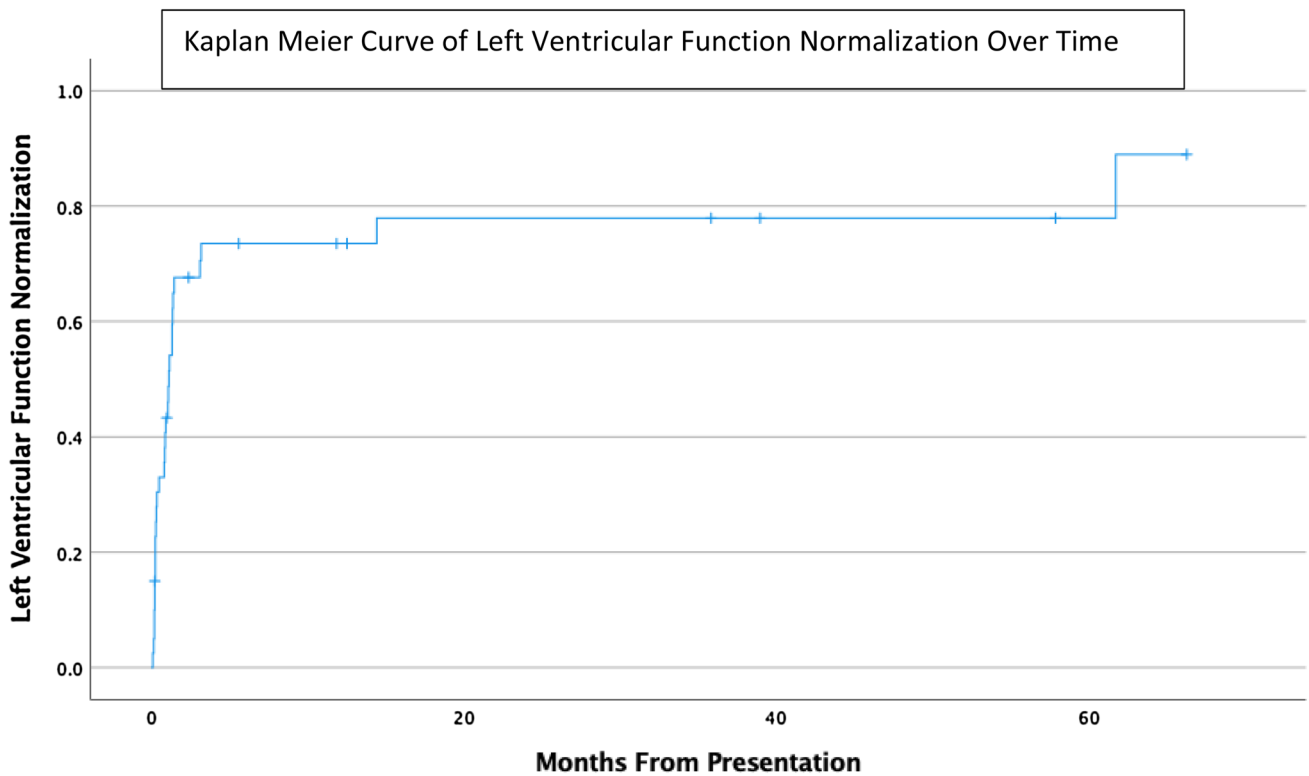
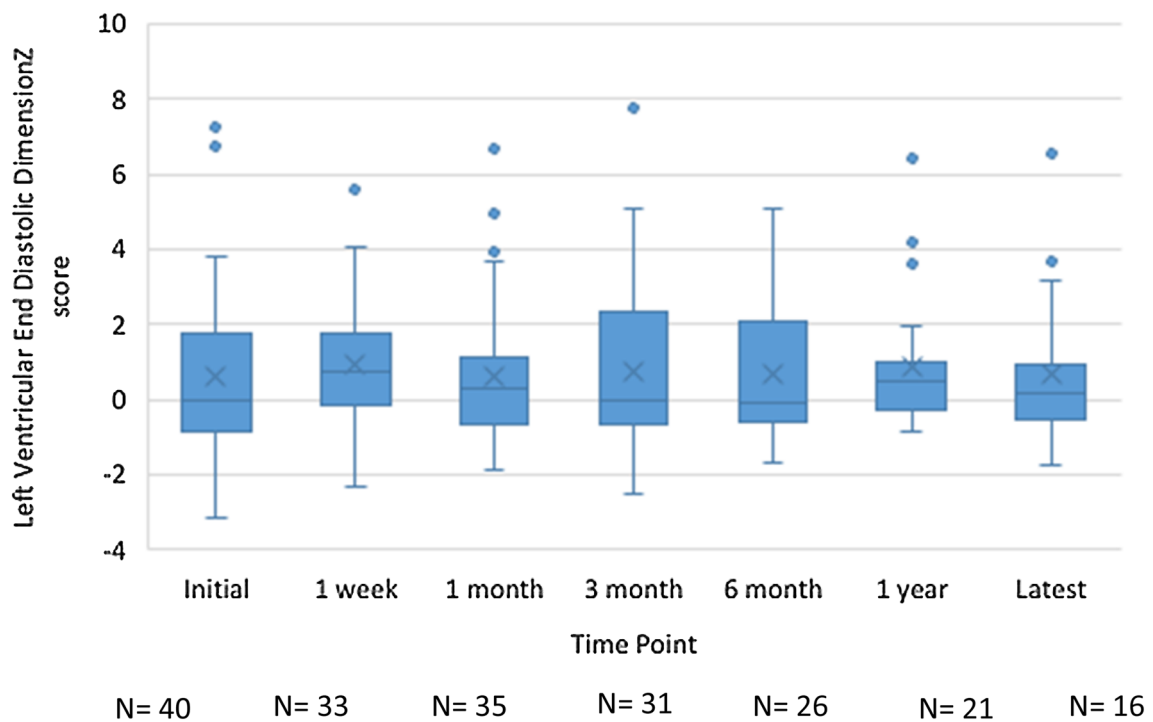**Fig. 1** Kaplan Meier Curve of left ventricular function normalization over time

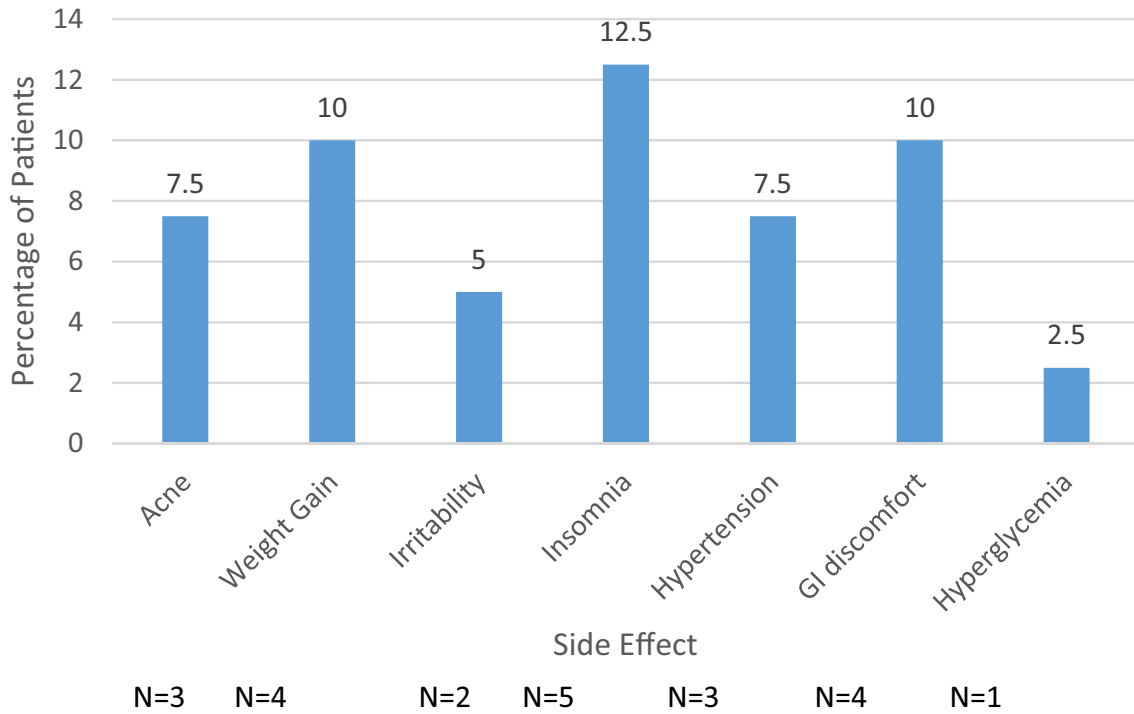**Fig. 2** Boxplot of left ventricular end diastolic dimension *Z* scores over time

Fig. 3 Perceived steroid side effects

Table 7 Medications at follow up

Follow-Up	Any Heart Failure Medication	Loop Diuretic	ACE-I /ARB	BB	MRA	Digoxin	Hydralazine/ISDN (Bidil)
Inpatient [N=40]	38 (95%)	32 (80%)	36 (90%)	17 (43%)	21 (53%)	2 (5%)	8 (20%)
Discharge [N=38]	36 (95%)	18 (47%)	33 (89%)	15 (40%)	14 (37%)	1 (3%)	4 (11%)
1-Month [N=35]	31 (89%)	12 (34%)	29 (83%)	13 (37%)	13 (37%)	1 (3%)	4 (11%)
3-Month [N=35]	33 (94%)	7 (20%)	31 (87%)	15 (43%)	11 (31%)	1 (3%)	3 (9%)
6-Months [N=31]	29 (94%)	3 (10%)	28 (90%)	13 (42%)	8 (26%)	1 (3%)	2 (10%)
12-Months [N=26]	23 (88%)	3 (12%)	23 (89%)	12 (46%)	6 (23%)	1 (4%)	1 (4%)
Latest Follow up between 3–5 years (Median 3.5 years) [N=19]	15 (79%)	2 (11%)	14 (74%)	7 (37%)	6 (32%)	1 (6%)	0 (0%)

ACE-I Angiotensin Converting Enzyme Inhibitor, *ARB* Angiotensin II Receptor Blocker, *BB* beta-blocker, *MRA* mineralocorticoid receptor antagonist.

normalization of their LVEDD z score by 1 month following presentation. Mitral and tricuspid regurgitation also improved over time with all patients having none or trivial regurgitation by 1 year follow up. There was no significant difference in recovery of function between patients with identified viral etiologies versus those without.

Follow-Up Medications

Eleven patients (27.5%) experienced adverse effects likely associated with steroids at follow up, including acne, weight gain, irritability, insomnia, hypertension, symptoms of gastritis and hyperglycemia. Details of adverse events are described in Fig. 3. Eight of these patients

(20%) had their steroid tapers modified during follow-up due to these associated adverse effects.

Most patients remained on a conventional oral heart failure regimen during follow-up. The most common component of the regimen was an ACE-I/ARB (Table 7).

Discussion

This study details our center's experience incorporating the use of high dose steroids with the more commonly used IVIG for treatment of acute myocarditis, and the management of the cohort by a single HF/TXP/MCS service. Under this regimen, transplant free survival in our cohort was 92.5% over a median follow up period of 1 year (IQR 0.5–3), with improvement in multiple echocardiographic indices of myocardial function observed over time. Additionally, we observed minimal significant adverse events in the setting of steroid administration with no overt propagation of any presumed viral infection.

There are multiple pathways of cardiac inflammation in myocarditis [16]. Liu et al. (2001) describe 3 phases of myocarditis starting with viral replication leading to autoimmune injury and finally to dilated cardiomyopathy. They posit that most patients will present with symptomatic myocarditis in the second phase and that the most appropriate intervention at this time is immune suppression unless the virus has not been controlled [17]. Steroids can help provide an immediate lympholytic and broad immunosuppressive as well as potent anti-inflammatory effect in this time frame to potentially stop the progression to dilated cardiomyopathy.

Though immunotherapy such as steroids are commonly used as part of treatment for myocarditis for these theoretical reasons [18], this has long been a controversial topic with lack of consensus in the literature. The most common cause of myocarditis in the United States is presumed viral infection, although a specific pathogen is often not identified [19, 20]. A Cochrane review [21] examined the role of corticosteroids in viral myocarditis in 8 randomized control trials with a total of 719 participants. While they found no difference in mortality between the corticosteroid and control groups, they found that EF was higher in the steroid group compared to the control group at 3 months. The results were inconclusive due to the heterogeneity of the studies. Only two of these studies included pediatric patients.

Li et al. (2019) performed a meta-analysis of 8 studies of pediatric patients with myocarditis who received IVIG or steroids. They found that IVIG seemed to improve LVEF and survival in children with myocarditis, while steroid treatment did not change outcomes [22]. They did not include patients who received both IVIG and steroids as received by our patients. These studies were small and without consistent treatment protocols, limiting the generalizability of the data.

Conversely, some studies have demonstrated at least a marginal benefit for immunosuppressive regimens in the pediatric population both at a clinical and histologic level. A small study of pediatric patients with myocarditis and ventricular arrhythmia treated with steroids showed improved arrhythmia burden. Authors of this study noted that arrhythmias seemed to recur when steroids were weaned [23]. Aziz et al. (2010) randomized patients at 3 months post myocarditis diagnosis to receive a prednisolone course compared to no steroids. They found that the steroid group had significant improvement in their LVEF over the intervening month while the control group did not [23]. Another study by Salvi et al. (1989) included 20 pediatric patients with biopsy proven myocarditis who were treated with prednisone and azathioprine, after which 15 saw complete disappearance of edema on follow-up biopsy [11]. Lee et al. (1999) studied pediatric patients with biopsy proven myocarditis who were treated with a similar steroid regimen to our protocol, although not all patients received IVIG. In this study, freedom from death or transplantation was 86% at one month and 79% at 2 years, less than in our cohort, although there was a higher reported frequency of echocardiogram normalization over time. It should be noted that all their cases were biopsy proven myocarditis and thus there is lower likelihood of inclusion of any idiopathic dilated cardiomyopathy cases [25]. Furthermore, our cohort is more contemporary with presumably an acute and largely severe form of myocarditis. It is possible that with delayed intervention or in the setting of chronic, indolent myocarditis there would be more LV remodeling, a memory lymphocyte response, or even persistent latent viral infection of the myocardium, where a burst of immunotherapy or even added maintenance immunotherapy may not be as effective. Compared to a prior study examining outcomes from the cardiomyopathy registry our patients had quicker normalization of systolic function by echocardiography (70% within 1 year in our study and approximately 50% in 3 years in the registry) and lower probability of transplant or death (6% vs nearly 20%) [26]. It is worth noting that only approximately 20 patients in the registry received steroid treatment despite a larger cohort and longer follow up period. There were also less stringent diagnostic criteria.

Recently, there has been significant attention to the use of steroids for myocardial dysfunction in COVID-19 related Multi System Inflammatory Syndrome in Children (MIS-C). A group of children treated with IVIG alone were compared to a group treated with IVIG and steroids during their acute presentation. The group that received steroids had a lower risk of need for hemodynamic support

and persistence of left ventricular systolic dysfunction as well as shorter intensive care unit stays [27]. This new entity of acute ventricular dysfunction with features of inflammation after a viral infection has similarities but clearly is not the same as the broad entity of idiopathic or presumed viral myocarditis.

Only a minority of our study cohort underwent biopsy, and only 1 patient had a positive PCR from biopsied myocardium. Several patients in our study, however, had positive respiratory or blood viral PCR suggesting recent or current viral infection. Importantly, we did not see any infection propagation amongst our cohort despite the use of high dose steroids. There has been suggestion that viral DNA on endomyocardial biopsy portends a worse prognosis for patients with myocarditis [27, 28]. Gagliardi et al. (2004) similarly found no significant new infections during their treatment of patients with myocarditis with prednisone and cyclosporine [30]. It is worth noting our patients and those in the Gagliardi study were all immunocompetent hosts, and care was taken prior to steroid initiation to ensure that infections were clinically under control.

We acknowledge that steroids are associated with potential side effects [11] and that 20% of our cohort experienced at least one side effect attributed to steroid use. These symptoms all resolved with alteration or earlier cessation of the steroid course. Overall, we feel that the risk of transient adverse effects associated with a 10–12-week steroid taper is less than the risk of developing lifelong cardiomyopathy or major adverse cardiovascular event from myocarditis. It is also feasible to adjust the taper especially after the initial high dose burst which the latter may have more impact in altering the course of LV recovery.

The approach we used to classifying myocarditis, and therefore whom to treat, reflects the practice in the real world, where further stratification on who receives immunomodulatory, anti-inflammatory, immunosuppressive, or no therapy in children is extremely challenging even in a properly designed prospective trial.

Study Limitations

This study has several limitations inherent to its observational study design. First, the small sample size and lack of a comparison group limited our ability to perform comparative analyses or attribute a treatment effect. Second, retrospective adjudication of the diagnosis of myocarditis is challenging. We performed stringent screening to improve the accuracy of our cohort selection, but it is possible some patients were inappropriately excluded or included. Additionally, we did not include patients that died prior to initiation of treatment

($N = 2$) or patients who were diagnosed with myocarditis as an outpatient or after the fact as the study is on the treatment of acute myocarditis with IVIG and steroids. Another limitation is lack of tracking inflammatory markers over the course of the study. Finally, although steroid treatment courses were largely consistent based on our protocol, there was some variation between patients when courses were modified for various clinical reasons. Lastly, the sample size is low, such that type I errors are clearly possible, and prevented comparative statistical analysis particularly when only 3 patients suffered a poor outcome.

Conclusion

Use of high dose steroids with IVIG to treat myocarditis in a contemporary cohort can be safe and in our experience was not associated with any apparent propagation of viral infection affecting clinical outcome. Our cohort had excellent recovery of ventricular function and survival without transplant (94%). Prospective comparison of a combination of high dose steroids with IVIG versus either therapy alone is needed.

Declarations

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