Fulminant Myocarditis

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This is to acknowledge that Dr. Mammen does not have a financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mammen will be discussing "off-label" uses in his presentation.

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Dr. Mammen is a member of the UTSW Heart Failure/Cardiac Transplant team. His clinical practice focuses on the treatment/management of patients with advanced forms of heart failure as well as patients who have undergone cardiac transplantation.

Dr. Mammen's scientific interests revolve around the discovery of the molecular mechanisms underlying heart failure. In particular, Dr. Mammen's laboratory investigates cardiac energetics, oxygen/nitric oxide metabolism and free radical biology in the heart under both physiological and pathophysiological conditions. Specifically, the laboratory is focused on the transcriptional regulation and functional roles of myoglobin and cytoglobin within the heart. Both myoglobin and cytoglobin are tissue hemoglobins that are upregulated in the injured heart. These tissue hemoglobins may serve to facilitate oxygen transport, act as oxygen sensors, scavenge free radicals, and/or maintain nitric oxide homeostasis within the cardiomyocyte. Utilizing homologous recombinant technology and biochemical/molecular/pharmacological assays, the laboratory is advancing our understanding of the functional roles of these tissue hemoproteins within the cardiomyocyte. An enhanced understanding of the transcriptional regulation and functional roles of myoglobin and cytoglobin will provide opportunities for the development of new therapeutic targets for the treatment of patients with advanced heart failure.

Introduction

Myocarditis is an inflammatory process that effects the myocardium resulting in ventricular systolic dysfunction and/or arrhythmias.[1,2] This clinical entity is marked by a lymphocytic invasion of the myocardium and is not an uncommon cause of acute onset heart failure. Its prognosis is variable and is dependent on the clinical presentation and the histopathology.

The development of myocarditis has been associated with a variety factors including infections, systemic diseases, drugs and toxins. The clinical course of a patient who develops a myocarditis follows one of two pathways:

1. acute non-fulminant myocarditis: The initial course may be insidious followed by an acute presentation of heart failure with the subsequent development of chronic myocarditis. These patients develop either chronic stable dilated cardiomyopathy or progress to advanced end-stage heart failure.

1. fulminant myocarditis: These patients present with acute, severe heart failure and are often in cardiogenic shock. If this clinical entity is quickly recognized and the patient is provided immediate mechanical ventricular support, a majority of these patients will have make a full recovery with minimal long term sequele.

The underlying pathophysiology resulting in either acute non-fulminant or fulminant myocarditis is similar. At this time the biologic and genetic factors that determine which clinical course a patient who develops myocarditis will proceed is not known.

The remainder of this clinical review will focus on fulminant myocarditis and its epidemiology, the underlying clinical presentation, methods of diagnosis, pathophysiology, management/treatment options and prognosis. Where appropriate, certain features of fulminant myocarditis will be contrasted to acute non-fulminant myocarditis.

Epidemiology

Myocarditis is not an uncommon cause of heart failure and it has been estimated that approximately 6-10% of patients with recent onset dilated cardiomyopathy is secondary to myocarditis.[3-6] In addition, approximately 20% of sudden death cases among young adults and athletes is due to myocarditis.[7-10] There are very few studies that have specifically reported the incidence and prevalence of fulminant myocarditis. McCarthy et al. demonstrated in a single center study that the incidence of fulminant myocarditis was approximately one case per year and the prevalence among a patient population with biopsy-proved myocarditis was

10%.[5] However, the prevalence of this clinical entity amongst a patient population referred to the authors' institution for workup of recently developed heart failure was 0.9%.

Clinical Presentation and Diagnosis

Clinical Presentation

Although the clinical features of patients with acute non-fulminant myocarditis may be variable, patients presenting with fulminant myocarditis have a sudden, abrupt onset of heart failure symptoms and marked hemodynamic compromise.[11] As illustrated in Table 1, many of these patients will have experienced flu-like symptoms (e.g. fevers, arthalgias, and malaise) within 2-4 weeks prior to presentation.[11,12]

Table 1: Baseline Clinical Characteristics of Patients With Fulminant and Acute Non-Fulminant Myocarditis[11]

Symptoms	Fulminant Myocarditis (n=11)	Non-Fulminant Myocarditis (n=43)
Flu-like illness within 4 weeks	100% (11)	21% (9)
Fever within 12 weeks	91% (10)	23% (10)
Acute onset of Sxs	100% (11)	56%(24)
NYHA Classification		
Class IV	73% (8)	58% (25)
Class III	27% (3)	26% (11)
Class II	0% (0)	16% (7)
Class I	0% (0)	0% (0)

Sxs, symptoms; NYHA, New York Heart Association

Laboratory Data and EKG

Leukocytosis, an elevated sedimentation rate, eosinophilia, elevated cardiac troponin T/I and/or an elevation in the cardiac fraction of creatine kinase will be present on the admitting laboratory data.[13-16] In addition, patients with fulminant myocarditis will often present with multiorgan failure (respiratory, renal and/or live failure) and this will be reflected in the laboratory data.

The presenting electrocardiogram may show alterations in normal conduction such as intraventricular conduction delays, high grade heart block, or ventricular arrhythmias.[17] Utilizing a multiple logistic regression analysis, Kato et al. assessed various risk factors for the development of fulminant myocarditis as compared to acute non-fulminant myocarditis.[15] This study discovered four predictors of fulminant myocarditis and they are as follows: 1. elevated C-reactive protein, 2. elevated creatine kinase, 3. intraventricular conduction delay, and 4. depressed left ventricular ejection fraction.

A study by Lee et al. found similar risk factors noted above for the development of fulminant myocarditis.[16] Finally, it has been purposed by Baronia et al. that abnormalities in venous oximetry may be another useful parameter to predict fulminant myocarditis.[18] In this case report the authors suggest a very elevated $\Delta S_{CV-MVO2}$ level [central venous oxygen saturation (S_{CVO2}) minus mixed venous oxygen saturation (S_{MVO2})] with a S_{MVO2} less than 65% on presentation should prompt the physician to consider fulminant myocarditis in the differential diagnosis of a patient in cardiogenic shock.

Differential Diagnosis

When an otherwise healthy individual presents with sudden cardiovascular collapse, one needs to be mindful of a few other key cardiac disorders in the differential diagnosis. Fulminant myocarditis can masquerade as giant cell myocarditis, necrotizing eosinophilic myocarditis, sarcoidosis, and peripartum cardiomyopathy (Table 2). Fulminant myocarditis has also been reported to mimic an acute myocardial infarction.[19] Therefore, it is essential to be able to distinguish these clinical entities from fulminant myocarditis as there are more definitive treatment options for a patient that presents with one of these disorders.

Table 2: Fulminant Myocarditis and the Differential Diagnosis

Differential Diagnosis of Fulminant Myocarditis	Key Clinical Features	Key Diagnostic Studies	Treatment
giant cell myocarditis	cardiogenic shock or malignant, persistent arrhythmias	Bx-infiltrate with multinucleated giant cells	combined immunosuppression or cardiac transplantation
necrotizing eosinophilic myocarditis	cardiogenic shock	Bx-diffuse inflammation with eosinophils & extensive myocyte necrosis	high-dose steroids
sarcoidosis	cardiogenic shock or malignant, persistent arrhythmias	Bx-presence of granulomas	high-dose steroids or cardiac transplantation
peripartum cardiomyopathy	acute onset CHF Sxs after pregnancy; may develop cardiogenic shock	clinical history associated with pregnancy	high-dose steroids; LVAD or cardiac transplantation for persistent shock
acute myocardial infarction	ST elevation on EKG	LHC revealing 100% coronary occlusion	coronary intervention (PTCA/stent) or thrombolytic therapy

Bx, endomyocardial biopsy; CHF, congestive heart failure; LHC, left heart catheterization; LVAD, left ventricular assist device; Sxs, symptom.

Giant cell myocarditis is often times associated with autoimmune disorders, thymomas, and drug hypersensitivity.[20-24] As compared to fulminant myocarditis, a greater percentage of patients with giant cell myocarditis present with ventricular tachycardia (16%), complete heart block (5%), or acute coronary syndrome (6%).[25] Therefore, if a patient presents in cardiogenic shock with the above symptoms, one needs to have a high clinical index of suspicion for giant cell myocarditis. A histological feature that distinguishes giant cell myocarditis is the presence of multinucleated giant cells on an endomyocardial biopsy sample. Clinically, these patients are often resistant to medical therapy. Unlike patients with fulminant myocarditis, patients with this clinical disorder may have a positive response to combined immunosuppressive therapy (cyclosporine and high-dose steroids); however, the definitive therapy for giant cell myocarditis is often cardiac transplantation.

Necrotizing eosinophilic myocarditis is a very rare disorder and has a very poor prognosis if immunosuppressive therapy is not initiated immediately.[26,27] The histological characteristic of necrotizing eosinophilic myocarditis is the presence of diffuse inflammation (predominantly eosinophils) and extensive myocyte necrosis.[28] Idiopathic hypereosinophilic syndrome, Churg-Strauss syndrome, malignancy, parasitic infections, and endomyocardial fibrosis can be associated with necrotizing eosinophilic myocarditis and therefore these systemic diseases need to be excluded.

Patients with cardiac sarcoidosis can also present in cardiogenic shock. Similar to giant cell myocarditis, the definitive treatment is cardiac transplantation, although some patients may respond to high-dose steroids. The pathological hallmark of this disease entity is the presence of non-caseating granulomas on the endomyocardial biopsy.[29]

Finally, patients with peripartum cardiomyopathy may present with a variety of clinical symptoms including hemodynamic instability. The underlying etiology of this disease process is not known but 78% of these patients have evidence of myocarditis on endomyocardial biopsy.[30] Immunosuppressive therapy or cardiac transplantation may improve long-term prognosis in these patients with evidence of myocarditis or persistent left ventricular dysfunction.

Diagnostic Studies Based on Histopathology

Although myocardial inflammation is a nonspecific response to various triggers (e.g. viral/bacterial infections, autoimmune disorders, cardiotoxic agents, and myocardial infarction), it remains a pathological hallmark of this disease entity. As such the endomyocardial biopsy persists as the "gold standard" for diagnosing myocarditis. In 1987, an expert panel of cardiac pathologists convened to develop the Dallas criteria, a classification system to standardize the interpretation of endomyocardial biopsies obtained to diagnosis myocarditis.[31] According to this pathological classification, specimens are classified as active myocarditis (routine light microscopy reveals infiltrating lymphocytes and

myocytolysis), borderline myocarditis (lymphocytic infiltrate but no myocytolysis), or negative (no evidence of myocytolysis or lymphocytic infiltrate).

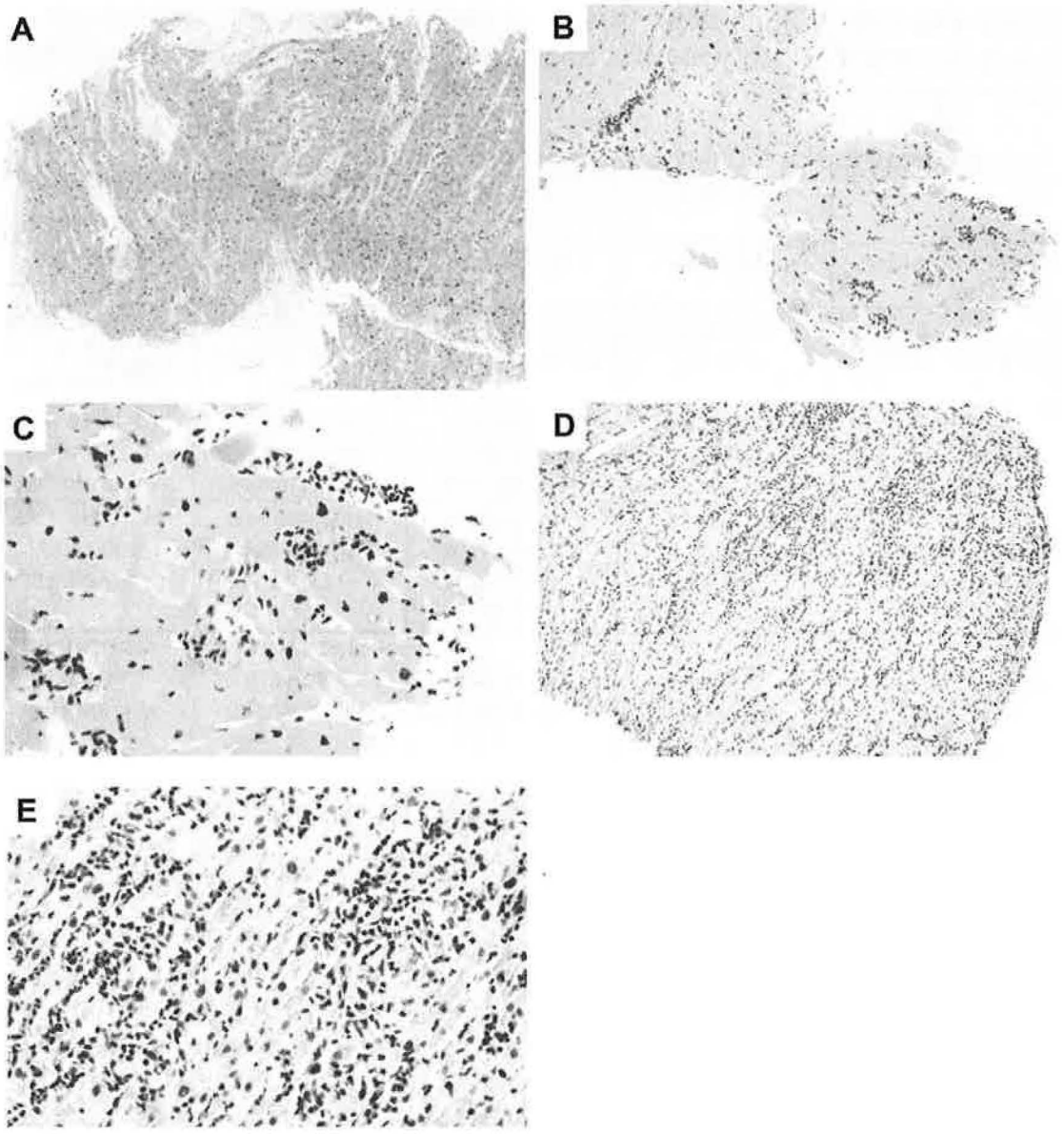


Figure 1: The Dallas Criteria for Myocarditis – Hematoxylin and Eosin Staining of Endomyocardial Biopsies (A) Normal myocardium (X100). **(B and C)** Borderline myocarditis (X100 and X350, respectively). **(D and E)** Active myocarditis (X100 and X300, respectively).

Due to the large degree of interobserver variability, the Dallas criteria underestimates the true incidence of myocarditis.[32] Although in general the Dallas criteria provides an exact histologic criteria for the presence or absence of myocarditis, it fails to provide long-term prognosis based purely on the histopathology. Therefore, in 1991 Lieberman et al. developed a second classification system based on the both the clinical course and the histologic

findings on the endomyocardial biopsy.[33] In this clinicopathologic classification, patients with suspected myocarditis were classified as having fulminant, acute, chronic active or chronic persistent myocarditis (Table 3). Lieberman et al. intended this new classification system to better predict the long-term clinical outcome of patients with myocarditis and identify patients who would benefit from immunosuppressive therapy.

Table 3: Clinicopathologic Classification of Myocarditis[33]

	Fulminant	Acute	Chronic Active	Chronic Persistent
Onset of Cardiac Sxs	Abrupt	Insidious	Insidious	Insidious
Initial Presentation	Cardiogenic shock	CHF Sxs and LV dysfunction	CHF Sxs and LV dysfunction	No CHF Sxs or LV dysfunction
Initial EMB	Multiple foci of active myocarditis	Active or borderline myocarditis	Active or borderline myocarditis	Active or borderline myocarditis
Clinical Natural History	Complete recovery or death	Incomplete recovery or chronic stable DCM	Progressive end-stage DCM	No CHF Sxs and nl LV function
Histologic Natural History	Complete resolution	Complete resolution	Ongoing or resolving myocarditis; fibrosis and giant cells	Ongoing or resolving myocarditis
Immunosuppressive Therapy	No benefit	Variable	No benefit	No benefit

CHF, congestive heart failure; EMB, endomyocardial biopsy; DCM, dilated cardiomyopathy; LV, left ventricle; Sxs – symptoms.

Diagnostic Studies Based on Various Imaging Modalities

Although results from an endomyocardial biopsy are highly specific for the diagnosis of myocarditis, the sensitivity of this test is very low (10-22%).[34,35] Therefore, there has arisen a need for accurate diagnostic imaging to support a clinical suspicion of fulminant myocarditis. At present there are four cardiac imaging modalities that are able to detect an inflammatory process within the myocardium and they are as follows:

1. Gallium-67 scintigraphy
1. Indium-111 anti-myosin antibody scintigraphy
1. Echocardiography (ECHO)
1. Cardiac magnetic resonance (CMR) imaging

Due to the poor specificity of both the Gallium-67 and Indium-111 anti-myosin antibody scintigraphy methods, the use of these imaging modalities to detect myocarditis has diminished over the recent years.

Echocardiography remains one of the primary imaging tools to assess left ventricular function and ascertain the presence of myocarditis in a patient presenting in cardiogenic shock. There have been numerous echocardiography studies that have been undertaken to identify key ECHO parameters to detect the presence of myocarditis.[11,36-42]

Felker et al. undertook a study to determine whether echocardiography could distinguish between fulminant and acute non-fulminant myocarditis.[11] In this study, 750 patients over a 7-year time span underwent endomyocardial biopsy as part of the workup to evaluate the development of idiopathic cardiomyopathy. Within this cohort of patients, 72 out of 750 patients (9.6%) were diagnosed with myocarditis based on the Dallas criteria. Utilizing the Lieberman clinicopathologic classification system, 11 patients were classified as having fulminant myocarditis while 43 patients were classified as having acute non-fulminant myocarditis. Combining a histologic grading scheme, hemodynamic data (obtained from a right heart catheterization), and ECHO data, there were several keys parameters that distinguished fulminant from acute non-fulminant myocarditis. These key parameters are listed below and the primary data from the study are noted in Table 4:

1. Severity of inflammation noted on the histology.
2. Heart rate.
3. Mean blood pressure.
4. Cardiac filling pressures (mean right atrial, pulmonary artery and pulmonary capillary wedge pressures).
5. Systemic vascular resistance index.
6. Left ventricular end-diastolic dimension.
7. Septal wall thickness.

Table 4: Histologic, Hemodynamic, and Echocardiographic Characteristic Data in Patients with Fulminant and Acute Non-Fulminant Myocarditis[11]

	Fulminant Myocarditis (n=11)	Acute Non-Fulminant Myocarditis (n=43)	p-value
Histology			NS
Myocarditis	100% (11)	77% (33)	
Borderline Myocarditis	0% (0)	23% (10)	
Severity of Inflammation			<0.01
Severe	55% (6)	5% (2)	
Moderate	45% (5)	14% (6)	
Mild	0% (0)	81% (35)	

	Fulminant Myocarditis (n=11)	Acute Non-Fulminant Myocarditis (n=43)	p value
Hemodynamics			
MAP (mmHg)	79±11	90±12	<0.01
Mean HR (beats/min)	109±21	91±21	<0.01
Mean RA (mmHg)	11±8	4±3	<0.01
Mean PA (mmHg)	28±11	21±9	<0.03
Mean PCWP (mmHg)	21±11	14±9	0.03
CI by THD ($L/min/min^2$)	2.8±0.9	2.5±0.6	NS
SVRI ($dynes*sec/cm^5$)	2,072±440	2,939±752	<0.01
PVRI ($dynes*sec/cm^5$)	244±242	218±150	NS
LVSWI ($g-m/m^2$)	21±11	31±14	NS
ECHO Parameters			
Fractional Shortening (%)	19±4	17±7	NS
LVEDD (cm)	5.3±0.9	6.1±0.8	<0.01
Septal Wall Thickness (cm)	1.2±0.2	1.0±0.1	0.01

NS, not significant. CI, cardiac index; LVEDD, left ventricular end-diastolic dimension; LVSWI, left ventricular stroke work index; MAP, mean atrial systemic pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RA, right atrial pressure; SVRI, systemic vascular resistance index; THD, thermodilution.

In another echocardiography based study, Mendes et al. assessed the prognostic value of right ventricular dysfunction in myocarditis.[38] In this study the authors did not distinguish between fulminant and acute non-fulminant myocarditis. Sixty percent of patients who presented with right ventricular dysfunction died or required cardiac transplantation compared to 0% in patients with preserved right ventricular function at 2 years. Utilizing a multivariate analysis the authors demonstrated that right ventricular dysfunction was the most powerful predictor of outcome in patients presenting with myocarditis.

Finally, there have been several recent studies investigating the role of cardiac magnetic resonance (CMR) imaging in the diagnosis of myocarditis.[43-51] Presently, CMR imaging is regarded as the most powerful noninvasive imaging modality to diagnose myocarditis. However, to date there are no studies investigating its ability to distinguish fulminant myocarditis from acute non-fulminant myocarditis. The reason for a lack of studies in this area likely is due to the fact that the majority of fulminant myocarditis patients require insertion of a mechanical ventricular assist device soon after presenting to the hospital and thus are not able to undergo a subsequent cardiac MRI.

Pathophysiology

Myocarditis is defined as an inflammatory process involving the myocardium and results from a variety of factors including infections, systemic diseases, and/or exposure to various drugs and toxins.[1,2] The underlying etiology and pathogenesis of fulminant and acute non-fulminant myocarditis is similar. Therefore, in this section a broad overview of the pathophysiology of myocarditis in general will be undertaken. A partial list of potential causes of this clinical entity are listed in Table 5.

Table 5: Potential Causes of Myocarditis[1,2]

Infectious Agents	Immune-Medicated	Drugs/Toxins
Bacterial	**Allergens**	**Drugs**
mycobacterial	cephalosporins	amphetamines
streptococcal species	colchicine	anthracyclines*
mycoplasma pneumoniae	digoxin	cocaine*
treponema pallidum	diuretics (furosemide, thiazides)	ethanol*
Fungal	isoniazid	**Heavy Metals**
aspergillus	phenytoin	copper
candida	penicillins	Iron
coccidiodes	small pox vaccine	lead
cryptococcus	sulfonamides	**Physical Agents**
histoplasma	tetanus toxoid	electric shock
Protozoal	tetracycline	hyperpyrexia
trypanosoma cruzi	tricyclic antidepressants	radiation
Parasitic	**Autoimmune**	**Miscellaneous**
schistosomiasis	Churg-Strauss syndrome	bee/wasp stings
larva migrans	IBD disease	scorpion bites
Viral	Kawasaki's disease	snake bites
adenovirus*	myasthenia gravis	spider bites
coxsackievirus*	polymyositis	
cytomegalovirus*	scleroderma	
encephalomyocarditis	SLE	
Epstein-Barr virus	thyrotoxicosis	
hepatitis C Virus	Wegener's granulomatosis	
HIV virus*		
influenza A & B Virus		
Paravovirus B19*		

* , The most common causes of myocarditis in North America and Europe.
HIV, human Immunodeficiency; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

Although there exists a variety of factors that may trigger the development of myocarditis, in North America it is believed the most prominent factor is related to viral infections. Utilizing polymerase chain reaction the viral genome has been identified within the myocardium in 10-20% of patients with active myocarditis.[5,52-55] It remains controversial whether infection with a specific virus is directly involved in the pathogenesis of myocarditis or whether it is caused by the subsequent inflammatory reaction that ensues after the initial viremia.

Our current understanding of the pathophysiology of myocarditis has been enhanced by several animal studies undertaken over the past 2 decades. The pathogenesis of myocarditis involves the activation of the host defense mechanism and follows 4 phases (Figure 2). The host defense mechanism is initially activated in order to limit myocyte injury/death; however, eventually this process becomes maladaptive leading to ventricular dysfunction.

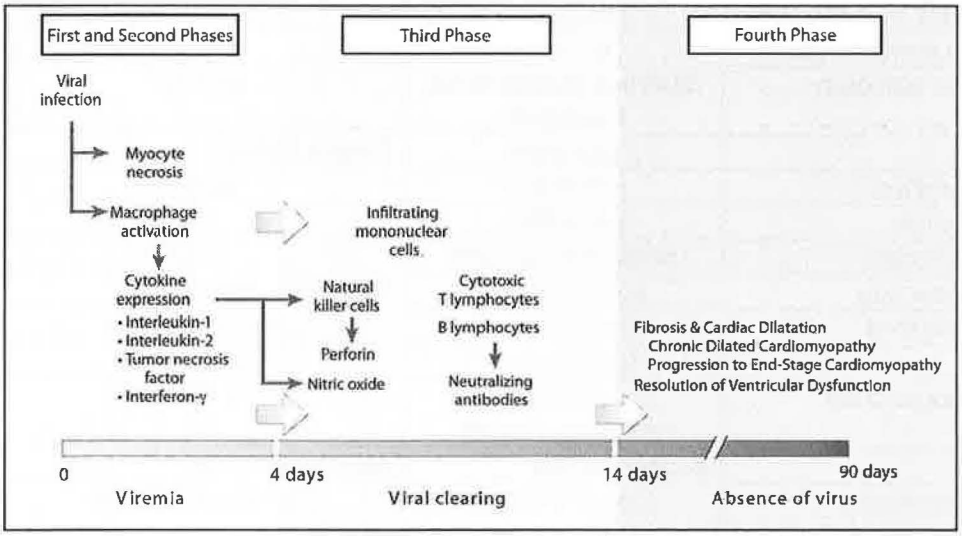


Figure 2: Proposed Pathogenesis of Viral Myocarditis.[1,56]

The initial phase of myocarditis involves a cardiotropic RNA virus, such as coxsackievirus B, directly being taken up into cardiomyocytes by receptor-mediated endocytosis resulting in the direct translation of viral proteins within the myocyte. It has been proposed that the viral proteins might result in direct viral-induced cytotoxic effects or myocyte dysfunction by cleaving the dystrophin complex and/or inducing apoptosis.[53,57] The second phase is marked by inflammatory cellular infiltrates (macrophages, natural killer cells, and mononuclear cells) into the myocardium resulting in the release of various cytokines (e.g. interferon-γ, interleukin 1 & 2, tumor necrosis factor) and nitric oxide. These proinflammatory cytokines serve to contain the viral infection but also have direct negative inotropic effects on the myocardium and may contribute to the development of pathologic left ventricular remodeling.[58-61]

Cell mediated immunity plays an important role in viral clearing and makes up the third phase in the pathogenesis of myocarditis. Antigen-specific T-cells (T helper and cytotoxic T-cells) are recruited to the infected myocardium.[56] These cells become activated by recognizing degraded viral protein fragments and exposure to co-factors released by antigen-presenting cells.[62,63] These activated cytotoxic T lymphocytes are now capable of lysing virus-infected cardiomyocytes.

The generation of neutralizing anti-viral antibodies and autoantibodies (directed against cardiac contractile, structural, and mitochondrial proteins) by activated B-cells enhances viral clearing. However, these antibodies especially the autoantibodies have detrimental effects on myocyte signaling transduction, calcium homeostasis within the myocyte and cardiac energy metabolism.[64]

Activation of the above host defense mechanism is required for the effective clearing of the virus and allows healing of the myocardium, resulting in resolution of the myocarditis (fourth phase). However, it is hypothesized that infection of genetically susceptible individuals with a certain virulent strain of virus may result in abnormal immunologic activity. As a result viral clearance may be ineffective, there may be persistence of activated T-cells, and/or continued antibody mediated myocyte destruction resulting in ventricular dysfunction.[1,56,65] It is in these susceptible individuals with myocarditis who will develop either chronic dilated cardiomyopathy or progressive end-stage heart failure.

Management and Treatment

Patients with fulminant myocarditis present to health care providers with hemodynamic instability and are often times in cardiogenic shock. Therefore, the first line of treatment is supportive care through the use of intravenous inotropic therapy, insertion of an intra-aortic balloon pump and/or implantation of a ventricular assist device. Initially, patients with this clinical entity should be started on intravenous diuretics to lower ventricular filling pressures and intravenous inotropic therapy to improve forward cardiac output. Insertion of either an intra-aortic balloon pump or mechanical assist device should be undertaken at a very early stage if the patient does not initially respond to intravenous inotropic therapy. There are several case reports and small studies demonstrating the short-term benefit of mechanical assist devices.[66-69] Mechanical ventricular support provided to a patient with hemodynamic instability has been shown to provide favorable alterations in cellular/organ geometry, reduce wall stress, and improve overall cardiomyocyte function.[70,71] Acker recently reported on the accumulative experience of mechanical ventricular assist devices in the setting of fulminant myocarditis and this data is presented in Table 6.[72]

Table 6: Mechanical Support for Fulminant Myocarditis: Types of Devices and Survival.[72,73]

Device	Number of Patients	Weaned to Recovery	Weaned Patients D/C	Need for Cardiac Tx	Tx Patients D/C	Survival
Extracorporeal Devices						
ECMO	37	73% (27)	96% (26)	0% (0)	0% (0)	70% (26)
PCPS	9	100% (9)	78% (7)	0% (0)	0% (0)	78% (7)
ABIOMED BVS5000	32	56% (18)	67% (12)	19% (6)	83% (5)	53% (17)
Thoratec VAD	40	40% (16)	88% (14)	45% (18)	94% (17)	78% (31)
Intracorporeal Devices						
TCI LVAD	17	12% (2)	NA	35% (6)	NA	47% (8)
Novacor LVAD	20	10% (2)	100% (2)	40% (8)	50% (4)	30% (6)

ECOM, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; PCPS, percutaneous cardiopulmonary support; TCI, Thermo Cardiosystems; Tx, transplantation.

The use of mechanical support devices for myocarditis accounts for less than 5% of devices implanted for hemodynamic compromise. Due to the presence of biventricular failure in many patients with fulminant myocarditis, the majority of the implanted mechanical support devices by ABIOMED and Thoratec are biventricular assist devices (BVAD). The overall survival rates of patients who underwent implantation of extracorporeal devices was 53-78%. On the other hand, patients who underwent insertion of intracorporeal devices had low overall survival rates (30-47%).

The choice of mechanical ventricular support in an otherwise healthy patient who is in cardiogenic shock of a non-ischemic origin should be dictated by the probability that the patient has fulminant myocarditis rather than giant cell myocarditis, necrotizing eosinophilic myocarditis, sarcoidosis, or peripartum cardiomyopathy. With supportive care, ventricular recovery usually occurs within several weeks after the onset of fulminant myocarditis. However, it remains difficult to predict which patient with fulminant myocarditis will acquire sustained myocardial recovery once the VAD is removed.[74]

Since every effort should be made to allow for full ventricular recovery, either the ABIOMED or Thoratec device should be inserted due to their ease in implantation/removal and the ability to provide biventricular support. The ECMO device also provides sufficient ventricular support in these patients; however, this device is associated with significant adverse events (e.g. peripheral vascular, hemolysis, and bedridden state).[75] The ECMO device is most beneficial in patients who present in cardiogenic shock or cardiac arrest and have severe respiratory failure with inability to oxygenate. In such a situation, ECMO will allow stabilization of the patient with initial neurologic, renal and pulmonary recovery. The use of intracorporeal ventricular devices should be limited to patients with

only left ventricular dysfunction requiring VAD support as a bridge to cardiac transplantation or as destination therapy. Figure 3 depicts a decision tree for selecting the most appropriate of mechanical support device.

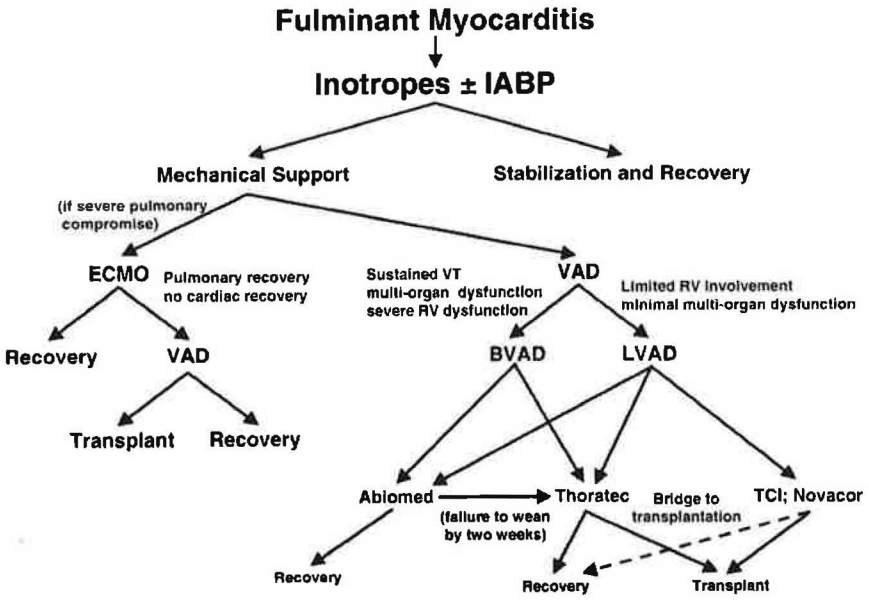


Figure 3: Selection of the Appropriate Mechanical Ventricular Assist Device for Fulminant Myocarditis.[72]

Once the VAD has been inserted and the patient is hemodynamically stable, standard medical care for heart failure should be initiated (e.g. ACE-inhibitors or ARB inhibitors, beta-blockers, aldosterone antagonists, and diuretics). However, digoxin should be used with caution as it increases the expression of proinflammatory cytokines and increases the mortality in a murine model of viral myocarditis.[76] If full myocardial recovery is achieved it is recommended the patient remain on the heart failure medical regiment indefinitively.

Finally, the utility of using immunosuppressive agents as adjunctive therapy for fulminant myocarditis remains unclear. Although myocarditis is an inflammatory disorder, there are only a limited number of randomized clinical trials assessing the efficacy of immunosuppressive therapy [e.g. steroids, intravenous immune globulin (IVIG), or interferon] on the resolution of myocarditis.[4,77-81] These trials have various limitations and all of these randomized trials have failed to demonstrate a beneficial effect of immunosuppression. In addition, none of these trials included patients with fulminant myocarditis. Therefore, the role of immunosuppression in the treatment of patients with fulminant myocarditis remains unknown. Due to the low incidence of this type of myocarditis, it is unlikely a well designed clinical study with the power to assess the role of these agents in the treatment of fulminant myocarditis will ever be undertaken. Data will need to be extrapolated from future double-blind, randomized, placebo-controlled trials involving acute non-fulminant myocarditis. The largest such trial is presently

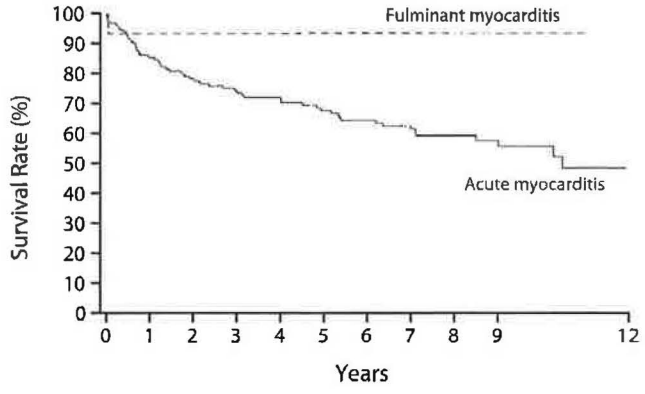
being undertaken and is called the European Study on the Epidemiology and Treatment of Cardiac Inflammatory Disease Trial (ESETCID).[6,82] In this trial there are a four treatment groups with corresponding placebo-control groups. The four treatment groups are listed below:

1. Prednisolone and azathioprine for autoreactive (virus negative) myocarditis.
2. Interferon-α for enterovirus-positive myocarditis.
3. High-dose IVIG for CMV myocarditis.
4. Intermediate-dose IVIG for adenoviral/paravoviral myocarditis.

This trial is ongoing and thus the outcomes of the trial are unknown at this time.

Prognosis

If early recognition of fulminant myocarditis can be made and the appropriate supportive care instituted in a timely manner, then long-term survival is good. McCarthy et al. reported on the long-term outcomes of fulminant myocarditis as compared with acute non-fulminant myocarditis at a single institution (Figure 4).[5] In this study one patient with fulminant myocarditis died and that was during the index hospitalization. The 1 and 11 year transplant-free survival percentage amongst patients with fulminant myocarditis was 93% and 93%, respectively. This was significantly better than patients with acute non-fulminant myocarditis who had 85% and 45% transplant-free survival 1 and 11 years after the initial biopsy, respectively.



No. at Risk

Acute myocarditis	132	110	98	91	84	79	73	59	41	28
Fulminant myocarditis	15	12	12	10	10	9	7	5	4	3

Figure 4: Unadjusted Transplantation-Free Survival Among Patients with Fulminant or Acute Non-Fulminant Myocarditis.[5]

Emerging Technologies and Novel Treatment Approaches

The ongoing advancements that are occurring in the understanding of the underlying pathophysiology of myocarditis will lead to new therapeutic targets for the treatment of both fulminant and acute non-fulminant myocarditis. Some of these novel targets and approaches are listed below:

1. Coxsackie-adenoviral receptor (CAR): The recent discovery that both the coxsackievirus and the adenovirus share a common receptor (CAR receptor) to infect a myocyte raises the possibility that pharmacological inhibition of this virus-receptor interaction could attenuate or halt the viral infection of cardiomyocytes. However, this approach presumes one is able to identify individuals susceptible to myocarditis during the early viremic stage.[83]

2. T-cell tyrosine kinase ($p56^{lck}$): Utilizing homologous recombinant technology, Liu et al demonstrated that $p56^{lck}$ knockout mice have improved survival after exposure to the coxsackievirus B3 strain.[84] Thus the T-cell tyrosine kinase, $p56^{lck}$, may serve as a future target for modulation in patients with myocarditis.

3. Vaccines against the coxsackievirus and/or adenovirus: Development of vaccines targeted against the most common viruses that cause myocarditis may prevent the adverse consequences of these viral infections. If effective vaccines could be developed, this approach should be incorporated into the childhood vaccine program, as children and young adults appear to have a predilection for myocarditis.[85]

4. Tolerance to autoantibodies: Development of specific autoantigens may result in immunologic tolerance and thus may serve as another potential target to attenuate the detrimental effects of myocarditis. In a mouse model of myocarditis, tolerance to myosin was achieved by the intranasal administration of cardiac myosin and thus suppressed the development of myocarditis.[86] Cardiac myosin is a common autoantigen that can initiate an autoimmune process during the third phase of myocarditis.[87-91]

Summary

Fulminant myocarditis is a rare cardiovascular disorder that has distinct histopathological features. Clinically, it is characterized by the rapid onset of hemodynamic deterioration in an otherwise healthy individual. If rapid recognition of this clinical entity is made and supportive care (e.g. intravenous inotropic therapy and use of mechanical ventricular assist devices) is initiated immediately, the long-term prognosis is good with full restoration of ventricular function.

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