

## Urgent Management of Acute Myocarditis

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### Abstract

**Background:** Myocarditis which is described as myocardial inflammation, Is a significant cause of severe cardiomyopathy and congestive heart failure. Clinical presentation of adult with acute myocarditis varies from subclinical case to fulminant heart failure, most of cases reports that before the onset of myocarditis by some days or few weeks, they complained fatigue, fever, rash, gastrointestinal and respiratory symptoms, they also revealed presence of dyspnea, palpitation, and chest pain that is similar to typical angina that is shown as changes in ECG, mainly as ST-segment elevation. To summarize, the presence of no limited range of symptoms and lack of specific diagnostic test made it hard to certainly know the incidence of myocarditis, but about 30% of those with acute myocarditis, develop heart failure and dilated cardiomyopathy that is affected most by the etiology of the case.

**Aim:** The objective of this article is to provide an up-to-date review regarding the prevalence, etiology, diagnosis, and urgent management of acute myocarditis.

**Conclusion:** Myocarditis is a potentially life-threatening disease for both adults and children and it could lead to death, although much progress has been made in diagnosis and treatment, some questions still needs more answer and we need to develop non-invasive and more specific diagnostic tools for rapid and accurate analysis, also more research should be done for more understanding of the cellular mechanism of the disease.

**Keywords:** Myocarditis; Acute Myocarditis; Urgent Management of Acute Myocarditis

### Introduction

Myocarditis which is described as myocardial inflammation, Is a significant cause of severe cardiomyopathy and congestive heart failure [1]. Position statement of the European Society of Cardiology defines myocarditis as a myocardial inflammatory disorder diagnosed by immunological, histological and immunohistochemical methods [2].

Histological criteria has been always done by the Dallas method; Which provides us with the histopathologic classification for myocarditis diagnosis, that gives a proof on presence of inflammatory infiltrate within the myocardium which is accompanied by both necrosis and degeneration of myocytes [3]. Unfortunately, this criteria is limited by many factors such as low sensitivity, absence of prognostic value and difference in experts' interpretation of the results [4]. Those drawbacks led to more advanced histological methods that depends on presence of certain markers such as anti-CD3, anti-CD4, anti-CD20, anti-CD28, and antihuman leukocyte antigen [5,6] on the other hand immunohistochemical.

Criteria defines myocarditis based on presence of equal to or more than 14 leucocytes per square millimeter, including up to 4 monocytes per square millimeter accompanied with CD3-positive T lymphocytes of equal to or more than 7 cells per square millimeter [7-9].

Myocarditis could be classified according to many approaches such as etiology, clinical type (acute, chronic or fulminant) and finally by cell type that could be (granulomatous type, lymphocytic or giant cell type) [10].

Clinical presentation of adult with acute myocarditis varies from subclinical case to fulminant heart failure, most of cases reports that before the onset of myocarditis by some days or few weeks, they complained fatigue, fever, rash, gastrointestinal and respiratory symptoms, they also revealed presence of dyspnea, palpitation and chest pain that is similar to typical angina that is shown as changes in ECG, mainly as ST-segment elevation [11]. Where a screening by the European Study of the Epidemiology and Treatment of inflammatory Heart Disease on 3055 case suspected with acute and chronic myocarditis revealed that 72% had dyspnea, 32% had chest pain, and 18% had arrhythmias [12].

To summarize, the presence of no limited range of symptoms and lack of specific diagnostic test made it hard to certainly know the incidence of myocarditis, but about 30% of those with acute myocarditis, develop heart failure and dilated cardiomyopathy that is affected most by the etiology of the case [13].

The objective of this article is to provide an up-to-date review regarding the prevalence, etiology, diagnosis, and urgent management of acute myocarditis.

### Prevalence

Although the true incidence of myocarditis is hard to be determined, the autopsy reports showed that the incidence of myocarditis to population ranges from 0.12% to 12% [14-16]. The treatment trials of myocarditis revealed that the patients with unexplained heart attacks showed incidence of 9.6% of myocarditis [17]. Also most studies showed that men are more subjected to myocarditis than women, this can be explained mainly due to sex hormones as, in female mice, estrogen has shown to protect against viral infection of myocarditis [18] and while in contrast, testosterone had a harmful effect as it inhibits the anti-inflammatory response [19].

The most affected population is the young adults as the patients with giant cell myocarditis have a mean age of 42 years [20], while other forms range from 20 - 51 years [21]. Sudden death also may occur in children due to myocarditis, as the risk of death and heart transplantation remains 12 years after child is diagnosed with myocarditis [22].

### Etiology

The causes of myocarditis could be summarized into three main causes: mainly infectious agent, mostly viruses, autoimmune disease and drugs. Myocarditis could be caused by infectious and non-infectious diseases, with viral infection as the main cause, enterovirus and adenovirus are identified as the main cause of myocarditis historically [23,24], recently parvovirus B-19 and human herpesvirus-6 became the main viruses related to myocarditis. In Japan, a relationship between hepatitis C and myocarditis recently appeared [25], also Human immunodeficiency virus (HIV) has been associated with myocarditis [26]. On the other hand the bacterial induced myocarditis is very less common and caused mainly by toxin-producing bacteria such as *Meningococcus* and *Streptococcus*.

Drugs may also cause myocardial inflammation either directly by toxicity or indirectly by hypersensitivity. Toxicity by anthracycline and cocaine are the most known causes of acute myocarditis [27,28]. Also, phenytoin and other medications can cause cardiotoxicity. While anticonvulsant and antipsychotic are related to hypersensitivity that causes mainly eosinophilic myocarditis, but fortunately the last case responds to medication withdrawal and adjuvant corticosteroid therapy [29].

Idiopathic myocarditis is rare, and presented mainly in two forms, the first is idiopathic GCM (giant cell myocarditis) known as virulent, autoimmune form of myocarditis [30], it is rare in adults and children too, and mostly accompanies immune-mediated diseases in other organs. The other form is Cardiac sarcoidosis [31], but it has a lower fatality rate than GCM [32].

### Pathophysiology

Many factors have been shown to affect viral myocarditis occurrence and virulence such as age, malnutrition, sex hormones and genetic host factor [33].

Pathophysiology of both viral and autoimmune myocarditis has been understood using rodent model infected with cardiotropic viruses as coxsackievirus. The first is firstly taken by endothelial receptor mainly in this case coxsackie-adenovirus receptor (CAR) [34], which is expressed more in brain and heart [35]. CAR is mostly found in intercalated disk of adult heart [36]. Viral infection causes innate immunity to work and cause upregulation of many inflammatory mediators such as complement, tumor necrosis factor (TNF) [36] and nitric oxide that causes viral induced-myocarditis, also the virus continues to replicate and produce viral proteins that cause myocardial injuries.

The acquired immunity, on the other hand can cause both viral and autoimmune myocarditis, as inflammatory infiltrates shown in myocardial lesion of myocarditis are composed of more than 70% monocytes, macrophage and T lymphocytes [37], acute myocarditis activates mainly acquired immune response that mediates the cardiac damage, where CD4+ T lymphocytes induces autoimmune myocarditis by production of cytokines, antibodies and autoantibodies [38].

Most patients with viral myocarditis, the virus is cleared by the immune system with no harm, but some cases the virus persists causing permanent damage to myocytes and myocardial inflammation.

### Diagnosis

Electrocardiogram is a non-specific diagnosis as it is used only to reveal abnormalities in the heart regarding ST-segment/T-wave changes [39]. While Echocardiography is the most important diagnostic test for acute myocarditis, it also enables us to exclude cardiac valve pathology [2]. Transthoracic echocardiography allows detection of global ventricular dysfunction. It is usually based on detection of transient wall thickening, systolic and diastolic dysfunction and finally reduced regional wall motion, so it is a very important diagnostic tool [40].

Nuclear imaging is not recommended due to its low specificity and variable sensitivity, except for cardiac sarcoidosis, as thallium 201 and technetium-99m scintigraphy may be useful for the diagnosis of cardiac sarcoidosis [41], also Cardiac magnetic resonance imaging could be useful in determining tissue characterization of myocardium [42].

Inflammatory markers as c-reactive proteins are raised during the acute myocarditis, but they are not specific, after that we moved to Cardiac troponins that seem to be more sensitive than creatine kinase in indicating myocardial injury and finally to the more sensitive and specific biomarkers like copeptin, circulating cytokines, pentraxin 3, or growth differentiation factor 15 [43]. While viral myocarditis is mainly confirmed with 4 times higher serum sample viral antibodies titer [43]

Finally, the Endomyocardial biopsy, which is still considered as the gold technique for analysis, as all the process toxic, inflammatory or autoimmune, they all occur at the cellular level. Also, EMB helps in revealing the cause of the myocarditis that affects the treatment of the case. The only concern regarding this method is the safety, but when done in experienced center, complications are rare, also it is recommended to have 2 - 3 samples and to perform analysis not only using classical techniques but also using immunohistochemistry and viral PCR to ensure better results [2,40].

### Management

The adult cardiomyocytes damaged by both viral and autoimmune myocarditis are rarely regenerated in adults, so the response for the treatment in both acute and chronic myocarditis depends on the cause of the disease, the severity of tissue damage, and the speed of treatment onset, so if the pre-treatment damage is high, the treatment will only prevent rapid progression but not improve the case.

**Heart failure therapy:** Standard heart failure therapy has proved efficiency in treatment of acute myocarditis especially when accompanied with DCM (dilated cardiomyopathy), including: diuretics such as angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors. Also digoxin could be used but with caution especially in viral-caused myocarditis as it increased the mortality [44], Amlodipine improved the histopathology of the lesion and survival in a study [45] and finally nifedipine also proved to be effective as it decreases the pro-inflammatory cytokines' activation [46]. Beside all the previously mentioned medications, intravenous inotropic medications could also be effective in acute myocarditis.

**Antiviral treatment:** It is logic that antiviral treatment could be effective in myocarditis, as most of the cases are mainly due to viral infection. The genome of the virus remains in a subset of patients with acute myocarditis. Data regarding treatment with antiviral medications are limited to some trials on murine models and a single case of a human. Treatment using interferon or ribavirin in murine decreased both the mortality and severity of the disease [47], while in human ribavirin did not show much effectiveness in acute myocarditis [48], while in patients with chronic DCM, treatment with interferon eliminated the viral genome and improved the case.

**Mechanical circulatory support and transplantation:** Mechanical circulatory could be effective with patients with cardiogenic shock because of acute myocarditis, whose case doesn't improve despite usage of medications [49]. Transplantation is only accepted when neither medications nor mechanical circulatory support are effective.

**Immunosuppressive treatment:** Many studies have been made on usage of immunosuppressant for treatment of acute myocarditis, but results were bad, as treatment using prednisone and azathioprine showed little or no effect [50], however usage of cyclosporine and corticosteroids improved the long term survival, but trust in the results is a little as the improvement could be due to the spontaneous recovery from the disease.

On the other hand, this treatment is very promising when dealing with chronic myocarditis as studies revealed that usage of azathioprine and prednisone had improved the left ventricular ejection fraction, so immunosuppressant could be beneficial to chronic myocarditis that resists medications [51,52].

**Intravenous immunoglobulin:** It could be effective in treatment of acute myocarditis that results from both viral and autoimmune disease, the recent modulation of acute myopathy showed that adults who were treated with IVIG, showed no improvement compared to placebo [53], while when used for children with acute myocarditis it improved the survival and the function of the left ventricle [54], so usage of IVIG is best recommended for children with acute myocarditis.

**Antiarrhythmic treatment:** It is mainly used with patients who develop sustained or symptomatic ventricular tachycardia, arrhythmia itself usually resolves after some weeks.

**Nonsteroidal anti-inflammatory drugs:** The usage of Nonsteroidal anti-inflammatory drugs in murine models showed no improvement in the case, on the opposite side, the case becomes worth if it is viral myocarditis as increased both inflammation and mortality [55].

**Physical activity:** Sudden death of young athletes due to acute myocarditis is the most proof the exercise during acute myocarditis is fatal and increases mortality, so patients with acute myocarditis are best advised to stay away from vigorous exercise [56].

## Conclusion

Myocarditis is a potentially life-threatening disease for both adults and children and it could lead to death, although much progress has been made in diagnosis and treatment, some questions still need more answer and we need to develop non-invasive and more specific diagnostic tools for rapid and accurate analysis, also more research should be done for more understanding of the cellular mechanism of the disease.

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