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Chapter
The Evaluation of Myocarditis in the Post-Covid-19 Era: Pearls and Perils for the Clinician
Daniel Zinkovsky and Michael R. Sood

Abstract

Coronavirus disease 2019 (COVID-19), which is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), continues to remain a global threat since declared a pandemic by the World Health Organization in March 2020. While primarily a respiratory disease, its clinical manifestations vary widely ranging from asymptomatic infection to multi-organ failure and death. As more research becomes available, cardiovascular involvement including acute coronary syndrome, heart failure, arrhythmias, thromboembolism, myocarditis and pericarditis have been reported in both the acute infectious stage as well as the post-symptomatic period. Myocarditis is an inflammatory disease of the myocardium that can result from infectious or non-infectious causes including autoimmunity, drug and toxin exposures. This chapter discusses the incidence, pathology, diagnostic modalities, and the management of myocarditis with a special focus on the essential role of a comprehensive approach, while utilizing advanced cardiac imaging for the assessment of myocarditis in the post COVID-19 era.

Keywords: cardiac MRI, CMR, COVID-19, Dallas criteria, endomyocardial biopsy, Lake Louise criteria, myocarditis, SARS-CoV-2 mRNA vaccine

1. Introduction

As of October 2022, the COVID-19 pandemic has been responsible for over 1 million deaths in the United States and over 6.5 million deaths globally [1, 2]. Its clinical manifestations range from asymptomatic to a mild, self-limited infection, to severe multi-organ failure and/or death. Due to the wide spectrum of illness and organ involvement as well as the diversity of cardiovascular manifestations and methods for its diagnosis, myocarditis can pose a particular challenge to clinicians.

Myocarditis is an inflammatory disease of the myocardium that can weaken the efficiency of the heart to pump blood or interfere with its conduction system. Most commonly, it occurs as a result from viral infection or autoimmune activation, toxins, drugs, or vaccine exposure. The diagnosis ranges widely and can be made based on history and various clinical aspects or via biopsy, which relies on an established criteria including histologic and immunohistochemical evidence. In 1986, the proposed
Dallas criteria established histopathological classifications to aid in the diagnosis of myocarditis requiring evidence of an inflammatory infiltrate with or without associated myocyte necrosis/fibrosis unrelated to ischemia [3]. Endomyocardial biopsy has remained the gold standard for diagnosis, despite recent advances in imaging technologies. However, postmortem analysis has revealed many limitations, stemming from challenges in specimens and sampling errors, in addition to variation in expert interpretation [4]. Furthermore, numerous studies have shown that a virus may be present in the myocardium in a replicative or non-replicative form in the absence of inflammation sufficient to meet the Dallas criteria [5, 6].

More commonly in clinical practice, a patient’s clinical symptoms, laboratory tests and imaging studies—including the use of cardiac magnetic resonance imaging (CMR)—is not only sufficient to establish a diagnosis but represents a non-invasive alternative to biopsy. CMR can detect early myocardial tissue response such as edema, hyperemia, and necrosis, as well as late consequences such as myocardial fibrosis and provide enhanced information that can be utilized in prognostication and clinical decision making [7].

2. Etiology/pathogenesis

The global incidence of myocarditis in 2017 was 3,071,000 cases, a 59.6% increase from 1990 according to data from the Global Burden of Disease Study 2017 [8]. However, the exact incidence is difficult to determine as myocarditis has a variable clinical presentation mimicking other conditions and can coexist with other cardiac or systemic diseases. Furthermore, there is limited availability of advanced cardiac imaging or endomyocardial biopsy, which can also contribute to confirming its diagnosis. Thus, the actual cases of myocarditis are believed to be significantly underestimated [9].

2.1 Infectious

Infectious causes remain the most frequent causes of myocarditis globally with viral etiology more common in the developed countries of North America and Europe, while bacterial, protozoal, fungal, and other rare pathogens are responsible for most cases in the developing countries of Africa, Asia, and South America [10]. A comprehensive list of currently identified infectious causes of myocarditis can be found in Table 1.

Bacterial myocarditis is rare, but the most common cause is *Staphylococcus aureus* and Streptococcal species [16]. The prevalence is difficult to determine with few studies published reporting 0.2–1.5% from cardiac biopsy samples post-mortem [17]. Furthermore, its prevalence has been shown to be more common in the setting of sepsis with or without concomitant endocarditis. The pathogenesis typically involves direct bacterial invasion into cardiac myocytes or by pathogenic toxins (common with clostridium or diphtheria). Cardiac dysfunction of either the left or right ventricle subsequently develops from severe sepsis (mediated by increased circulating cytokines), myocardial inflammation/necrosis, direct action from toxins and in the later stages, ventricular remodeling.

Viral myocarditis is by far the most common etiology with an incidence in the range of 10–22 per 100,000 individuals [18]. The pathogenesis follows a similar course of other pathogens that involve direct myocardial invasion with three distinct
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phases: acute, subacute, and chronic. Each phase is characterized by a distinct process with variable transitional periods. In phase 1 (acute), the virus gains access into the target organ tissue and triggers an immune response. This may progress into phase 2 (subacute), an autoimmune phase involving autoreactive T-cells, cytokines, and cross-reacting antibodies predominant after the full or partial resolution of the initial infection. Finally, in phase 3 (chronic), there is progressive remodeling often from autoimmune injury to the myocardium resulting in a persistent or often dilated cardiomyopathy [18, 19].

The acute phase includes the first days following infection where viral replication occurs within the heart and other organs. Viral entry is largely facilitated by specific receptors that vary based on the pathogen. For instance, Measles virus entry depends on the major revorius receptor JAM-A, SARS-CoV-2 utilizes the spike protein to bind the ACE2 receptor and in Group B coxsackieviruses (CVB) viral entry is mediated via two host receptors, decay-accelerating factor (DAF) and coxsackievirus-adenovirus receptor (CAR). In the case of coxsackievirus, these receptors are expressed in cardiac myocytes and pancreatic cells. Animal models have demonstrated the important role they play in so much that targeted deletion of these receptors is protective against CVB-induced pancreatitis and myocarditis [20]. Following initial viral entry, the virus causes cell lysis and spreads infection to adjacent cells through release of packaged virions. The cardiomyocyte injury triggers an innate immune response increasing the levels of cytokines and infiltration of immune cells into the damaged tissue (seen in Figure 1).

Approximately 1 week following infection, the subacute, autoimmune phase develops in response to the immune dysregulation caused by myocyte injury via molecular mimicry of the viral antigens to host cardiac proteins [22]. It should be noted that acute reduction in LV function along with hemodynamic compromise can occur during acute and subacute phases. The constant activation of T cells, increased levels of cytokines including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, Viral

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Infectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoviruses, HBV, HCV, HHV6, HSV 1 and 2, Chikungunya virus, SARS COV-2, Coxsackie virus, Dengue virus HIV, CMV, EBV, Influenza, Parvovirus B19, Measles virus, Mumps virus, Polioviruses, Rabies virus, Respiratory syncytial virus, Rubella virus, Varicella-Zoster virus, Variola virus, Vaccinia virus, Yellow fever virus</td>
<td></td>
</tr>
</tbody>
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Table 1. Infectious causes of myocarditis [11–15].
and IL-6, may lead to persistent and recurrent myocardial damage causing further impairment of the heart's contractile function and progressive remodeling, which is seen in the chronic phase of the disease.

In the final, chronic phase of the disease, the cumulative effect of the virus either through direct cytotoxic or subsequent autoimmune damage initiates a process of myocardial remodeling that can lead to dilated cardiomyopathy. In most cases by the chronic stage, the virus has been cleared and inflammation subsided, but in some cases the chronic phase is associated with a persistent viral infection and ongoing autoimmune responses. In myocarditis patients with chronic symptoms and inflammation, parvovirus B19 (PVB19) and human herpesvirus 6 (HHV6) genomes predominate in EMB samples with approximately 30% of patients having multiple viral infections [23].

2.2 Drug/toxin induced

Toxic drug-induced myocarditis is inflammation of the myocardium from drugs used as part of medical treatment or recreation. Damage is often by direct cytotoxic effect and/or immune-mediated but in many cases the concomitant mechanisms are poorly understood. Table 2 lists many of the currently identified drugs/toxins reported to induce myocarditis with a recent analysis of World Health Organization pharmacovigilance database recognizing five distinct categories of drugs: antipsychotics, cytotoxic drugs, immunotherapies, vaccines, and salicylates [11–15, 24–30]. Although patients are not routinely screened, they share many distinct similarities in presentation and clinicians should have heightened awareness to such etiologies. Cardiac injury can be either acute or progressive but frequently irreversible (even if
recognized early in its course), manifesting with new onset arrhythmias, a bundle branch block and in its end stage as an idiopathic dilated cardiomyopathy. Like other causes, resulting inflammation and myocyte destruction gives way to fibrous tissue replacement. In the case of antipsychotics such as clozapine, it is believed that a type 1 hypersensitivity reaction to clozapine itself or its cardiotoxic metabolite triggers a rise in inflammatory mediators [31].

Immune checkpoint inhibitors (ICI) which enhance T-cell mediated immune responses for the treatment of a variety of malignancies are effective but are associated with either fulminant or insidious myocarditis. While the incidence of myocarditis with these agents is rare, ranging from 0.27% to 1.14%, it is associated with a high mortality rate of 40–50% in those affected [32]. The risk was greatest with the combination therapy utilizing anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA-4) and anti-programmed cell death 1 (anti-PD 1) agents. ICI-associated myocarditis is unique histologically demonstrating myocardial infiltration of T lymphocytes and macrophages with direct involvement of the conduction system leading to more observed arrhythmias upon presentation with a lower incidence of heart failure when compared to other forms of myocarditis such as viral and autoimmune in which inflammation ultimately leads to dilated cardiomyopathy [30].

Hypersensitivity reactions with eosinophilic myocarditis are associated with both antipsychotic agents and salicylates while ICIs are associated with lymphocytic myocarditis (Figure 1). Direct cardiac cytotoxicity, apoptosis and free radical oxidative damage are predominant features of cytotoxic antineoplastic agents. Vaccine associated myocarditis, on the other hand, such as seen with smallpox is primarily an autoimmune mediated response from the vaccine’s ability to mimic myocardial antigens [11].

2.3 Autoimmune

While immune activation has a prominent role in the pathophysiology of myocarditis secondary to infectious or selected drug-induced process as previously described, systemic immune-mediated diseases that include systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), vasculitis (such as eosinophilic granulomatosis and polyangiitis (EGPA)), sarcoidosis and even organ-based immune mediated diseases such as chronic inflammatory bowel diseases may be associated with myocarditis [33].

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Phenothiazines, Tricyclic antidepressants, Lithium, Clozapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td>Smallpox, Influenza, Anthrax, DTPP, HepA/HepB, Meningococcal, COVID-19</td>
</tr>
<tr>
<td>Immunotherapy (including Immune Checkpoint inhibitors)</td>
<td>Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Avelumab, Cemiplimab</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>5-Fluorouracil, Anthracyclines, Cyclophosphamide</td>
</tr>
<tr>
<td>Salicylate</td>
<td>Mesalazine, Sulfasalazine</td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>Amphetamines, Cocaine, Alcohol, ephedrine</td>
</tr>
<tr>
<td>Cardiac medications</td>
<td>Dobutamine, Epinephrine, Norepinephrine, Dopamine</td>
</tr>
</tbody>
</table>

Table 2. *Drugs/toxins known to cause toxic myocarditis [11–15, 24–32]*.
Eosinophilic myocarditis can be seen with autoimmune diseases (SLE, EGPA, inflammatory bowel disease), hypersensitivity to select medications (antibiotics, sulfa-drugs, anticonvulsants, diuretics), hematologic nonmyeloid malignancies (lymphoma, acute myeloid leukemia, acute lymphoblastic leukemia) as well as infectious (parasitic, fungal, HIV) causes [34]. It should be suspected in patients with peripheral blood eosinophilia >1.5G/L and symptoms of acute coronary syndrome or heart failure but without obstructive coronary disease. Additional clues may include rash or elevated liver function tests. Rate of death or cardiac transplantation with a fulminant presentation of eosinophilic myocarditis can exceed 26% in only 60 days [35]. A resulting cardiomyopathy proceeds along three stages progressing from (1) infiltration of myocardium by eosinophils, (2) thrombosis driven largely by endomyocardial damage and alteration of systemic coagulation via enhanced tissue factor expression and impaired thrombomodulin, (3) biventricular endomyocardial scarring and fibrosis from activation of cardiac mast cells to the released eosinophilic granules [36].

Giant cell myocarditis (GCM) on the other hand, is associated with thymomas, inflammatory bowel disease, autoimmune disorders, drug hypersensitivity and is considered among the most fatal forms of myocarditis with studies indicating a rate of death or cardiac transplantation of approximately 70% [37]. In particular, giant-cell myocarditis has been shown to be histologically similar to cardiac sarcoidosis. A retrospective audit of 73 cases of GCM diagnosed in Finland since the late 1980s found that 60% of the original GCM diagnoses required conversion to cardiac sarcoidosis [38]. Myocardial necrosis and granulomas are present in both cardiac sarcoidosis and GCM although necrosis is typically more extensive in GCM where both eosinophils and lymphocytes are found in higher numbers, while granulomas are more common in cardiac sarcoidosis which has a greater extent of myocardial fibrosis [39]. This overlap is important to consider when the early diagnosis of GCM with calcineurin based immunosuppressive therapy can reduce the complications and mortality over cardiac sarcoidosis in which the mainstay of treatment consists of glucocorticoids.

Systemic lupus erythematosus (SLE) is another autoimmune disease commonly with cardiac and extracardiac involvement. Cardiac injury can occur from immunological injury, ischemia from accelerated atherosclerosis, as well as valvular disease from immunoglobulin and complement deposition. Although pericarditis is more common, lupus myocarditis occurs at a prevalence of 9% but is believed to have a higher prevalence in a subclinical form with 57% seen on autopsy [40]. Given the heterogeneous cardiac manifestations in systemic immune-mediated diseases, screening for autoimmune disease is recommended in patients with clinically suspected myocarditis for prompt diagnosis and appropriate management [41].

2.4 COVID-19/COVID vaccine

Recent studies estimate the incidence of cardiac injury ranging between 7 to 30% of patients with COVID-19 [33, 34]. This cardiac injury is believed to be multifactorial, caused by direct viral infection of the myocardium, complications from the widespread systemic inflammatory response, in addition to the prothrombotic changes including plaque rupture, demand ischemia or vasospasm [35]. The variability in symptoms and complications of SARS-CoV-2 infection has been presumed to be the result of the viral spike protein's utilization of its functional receptor, the angiotensin converting enzyme-2 (ACE-2), which has widespread expression on pulmonary alveolar cells, cardiac myocytes, gastrointestinal epithelial cells, and
vascular endothelial cells [36]. Determining the true incidence of myocarditis is challenging, limited by the lack of endomyocardial biopsy in many presumed cases which would allow for histological confirmation or isolation of SARS-CoV2 virus in the myocardium.

In a meta-analysis of 31 case studies including 51 patients with suspected COVID-19 associated myocarditis, males were more commonly affected (69%) with a median age of 55 years (range 28–60 years) [37]. Another cohort single center study of 416 patients hospitalized with COVID-19 had an older median age of 64 years and balanced gender distribution with females affected at 50.7%. Of the total patients, 19.7% had cardiac injury, which tended to be older (median age 74), with more comorbidities (59% had hypertension), that commonly required noninvasive mechanical ventilation, had more complications (acute respiratory distress syndrome, acute kidney injury, electrolyte disturbances, coagulation disorders) and had a higher mortality than those without cardiac injury (51% vs. 4.5%) [38]. Numerous autopsy studies had demonstrated the widespread distribution of SARS-CoV-2 viral infiltration and replication in various body tissues including the respiratory tract, brain and cardiac myocytes [39, 40]. The virus can persist in these tissues without a concomitant inflammatory or immune mediated response.

Following widespread COVID-19 vaccination efforts specifically with the SARS-CoV-2 mRNA vaccines, myocarditis and myopericarditis cases were increasingly being reported in the literature. The estimated incidence ranges from 4 to 29.8 cases per million doses, most commonly seen in males aged ≤40 years following the second dose and presenting with symptoms on day 3 through 7 post-vaccination. The mechanism behind vaccine induced myopericarditis is believed to be caused in part by molecular mimicry of antibodies against SARS-CoV-2 spike protein and a self-antigen, increased IL-18-mediated immune responses and aberrant induction of apoptosis [41]. It is not associated with eosinophilia, thrombosis or mast cell activation.

3. Clinical presentation/diagnosis

Due to a varied clinical presentation and potential insidious processes of myocarditis, ranging from asymptomatic to congestive heart failure, hemodynamic compromise with shock or death, the diagnosis can be a challenge for the experienced clinician. The severity of clinical presentation can serve as a potential predictor of the prognosis with those exhibiting hemodynamic instability and or systolic dysfunction (LVEF < 50%) on admission suffering the highest risk of death or need of transplantation [42].

The most commonly presenting symptoms include fever, shortness of breath, cough, and chest pain (which can often overlap with pericarditis) or Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA) type syndrome, associated with elevated troponin on labs and regional wall motion abnormalities on echocardiogram. These patients tend to have generally good outcomes as opposed to other presentations of myocarditis that include heart failure (or acute cardiomyopathy), ventricular tachycardia, heart block or sudden death.

A patient with suspected myocarditis may present with a constellation of abnormal findings on laboratory, ECG, Echocardiogram and cardiac MRI. On ECG, many patients demonstrate non-specific ST segment and T wave changes that are present in addition to ventricular tachycardia or premature ventricular complexes. Elevated cardiac (Troponin, NT-pro-BNP) and inflammatory biomarkers (WBC, IL-6, CRP) are
common as well as left ventricular dysfunction and hypokinesis on echocardiogram [37]. In the multicenter ITAMY study of 386 patients with acute myocarditis, most patients were young males (75% male, average age of 35), with preserved LVEF (62%) presenting with chest pain (95%), troponin elevation (100%, average peak 1.85 ng/ml), ECG abnormalities (96%), and wall motion abnormalities on echo (21%). An anteroseptal pattern on CMR was most associated with increased risk of major cardiac events (MACE) when compared to the inferolateral pattern which had the lowest risk of any LGE pattern [43]. Despite the gold standard diagnosis via myocardial biopsy, there is not one specific diagnostic criterion for the evaluation of myocarditis and advancements in cardiac imaging have led this evolution [44]. Therefore, a comprehensive evaluation is prudent and thus, we will discuss various imaging modalities further in this section.

3.1 Laboratory studies

To identify patients with suspected acute myocarditis, initial workup may involve laboratory tests for biomarkers of cardiac injury (troponin I, creatinine kinase-MB (CK-MB), Natriuretic Peptides (BNP or NT-proBNP)), inflammatory markers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), and differential white blood cell count (which can reveal eosinophilia) are routinely recommended. However, despite the availability of cardiac and inflammatory biomarkers, these may pose a challenge in the diagnosis of myocarditis as each of these markers, respectively, may be elevated in response to systemic illness (such as from tachycardic states, catecholamine excess, hypoxia driven myocardial stress and/or dysfunction), or other extra-cardiac organ dysfunction such as anemia or renal failure. Therefore, the utilization in surveillance of such biomarkers in relation to other clinical parameters (symptoms, physical examination, timing) and various imaging modalities, comprehensively, is recommended.

Troponin I has been shown to be highly specific (89%) but has limited sensitivity (34%) and superior to CK-MB in the diagnosis of myocarditis [45]. CK-MB elevations occur less frequently than troponin elevations in acute myocarditis. Plasma BNP, a cardiac neurohormone released in response to increased ventricular stress, is an important laboratory marker with a high positive predictive value for the diagnosis of heart failure. Like other biomarkers, it has been shown to be elevated in other cardiac etiologies such as acute coronary syndrome [46]. In acute myocarditis, patients with high baseline NT-proBNP had the highest rate of major adverse cardiac events both at 30 days and up to 3 years follow up, suggesting higher levels are predictors of poor outcomes [47]. Similarly, in the case of COVID-19, NT-proBNP is commonly elevated and high levels were significantly correlated to increased risk of death [48]. Inflammatory markers such as CRP are positive in 80–95% of cases of myocarditis in addition to ESR, in which persistent elevations could suggest an underlying autoimmune disorder [49].

Other less common serologic tests or virological tests can be considered to narrow the differential diagnosis in select patients presenting with myocarditis from infectious or autoimmune causes which include, HIV and Borrelia burgdorferi antibodies, polymerase chain reaction from samples of the respiratory tract (influenza and SARS-CoV-2), and autoantibodies (antinuclear antibodies) to name a few.

3.2 ECG

Myocarditis can present with a multitude of electrocardiographic (ECG) abnormalities across a spectrum of tachy- or bradyarrhythmia. Mechanisms for these
observed changes are believed to result from direct myocardial damage, high catecholamine states with elevated sympathetic or parasympathetic tone, and conditions of high interleukins or inflammatory-mediated myocardial damage. These conduction alterations may also be associated with concomitant structural abnormalities such as left or right ventricular chamber dilatation in various stages of myocarditis. Sinus tachycardia associated with nonspecific ST/T-wave changes are the most common ECG findings in myocarditis, while patterns of PR segment depressions in leads with ST segment elevation (STE), precordial and limb leads, or a PR segment elevation in aVR generally favors the diagnosis of pericarditis or peri-myocarditis (Figure 2). STE and T wave inversions (TWI) may be evident in various phases of myocarditis due to varying voltage difference in depolarization and repolarization exhibited between the epicardial and endocardial layers in the setting of myocarditis. Often this may overlap with STE mimicking that of ischemic injury pattern from obstructive coronary artery disease or pericardial involvement. Reports have also shown STE on presentation similar to that of an acute STE myocardial infarction without any proven obstructive coronary artery disease, and where the initial ECG findings and STE corresponded to areas of non-ischemic scar pattern seen later on CMR (Figure 3) [51].

In a study of 800 patients with COVID-19 at Mount Sinai Hospital, VT or VF contributed to 11% of the mortality [53]. Additionally, a small retrospective study of 275 patients presenting to the emergency department with COVID-19 found most ECGs were in normal sinus rhythm, with 10% of patients having atrial fibrillation/flutter, and another 40% with repolarization abnormalities including negative T waves in 21% of all abnormalities. The finding of an abnormal axis or left bundle branch block was significantly associated with in-hospital mortality [54].

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study including 751 patients with COVID-19, STE were rare findings, while other ECG abnormalities such as the presence of one or more atrial premature contractions, a right bundle branch block or intraventricular block, ischemic T-wave inversion and nonspecific repolarization increased the odds of death [55].

3.3 Imaging

3.3.1 Echo

Echocardiography is often the initial imaging modality utilized in patients presenting with cardiac complaints due to its wide availability and lower costs. It can be performed non-invasively and at a patient’s bedside. While findings can be nonspecific, it is useful in the diagnosis of heart failure and can determine patterns of dilated, hypertrophic, restrictive, and ischemic cardiomyopathies. It is also effective to easily exclude emergent cardiac conditions such as cardiac tamponade, acute mitral regurgitation, and other states of hemodynamic compromise, all of which may be secondary complications of myocarditis. Myocarditis may cause segmental or global dilatation of the Left Ventricle, focal thickening of the ventricular wall, regional wall motion abnormalities, pericardial effusion, and focal interstitial edema of the myocardium. Right Ventricular dysfunction is associated with increased morbidity and mortality and a higher need for heart transplantation. In a study of 42 patients with biopsy-proven myocarditis, 23% of the patients had evidence of RV dysfunction which was associated with a worse prognosis [56].

Patients with obesity or chronic lung diseases pose a well-known limitation of echocardiography, due to a poor acoustic window which leads to an inadequate assessment of cardiac function and structure [57]. Similar to laboratory markers, the...
delineation of abnormal echocardiographic findings such as chamber dilatation or reduction in left or right ventricular systolic function as a result of demand related stress from systemic or critical illness (such as from hypoxia, tachycardia, anemia) vs. myocarditis can be a challenge. In general, acute cases of myocarditis have subtle echocardiographic features, including focal wall motion abnormalities and mildly reduced ejection fraction [58].

3.3.2 CMR

Cardiac magnetic resonance (CMR) continues to further advance the diagnostic capabilities possible in heart disease. The lack of ionizing radiation and newer contrast agents that are exclusive of contraindications in those with compromised renal function make it a safe imaging modality to a wider variety of patients. The agent used is often gadolinium, which in a healthy myocardium with intact cellular membranes tends to clear at a higher rate when compared to damaged cardiac tissue. In an acute myocardial infarction, ruptured cellular membranes tend to have delayed clearance of the contrast agent, and in tissues with signs of chronic damage such as myocardial fibrosis the contrast agent becomes confined within the collagen matrix of the scar causing a specific finding on CMR known as late gadolinium enhancement (LGE).

Myocardial fibrosis can be seen in a variety of cardiac diseases oftentimes in characteristic patterns. Subendocardial or transmural fibrosis patterns are often seen after an ischemic event such as a myocardial infarction where damaged tissue becomes replaced with fibrosis. Several diseases have multiple overlapping patterns such as sarcoidosis and myocarditis that can appear with mid-wall or epicardial patterns as a result of reactive interstitial fibrosis. Sparing of the subendocardial border in non-coronary distributions are hallmark features exhibited in non-ischemic scar patterns [59].

The diagnosis of myocarditis using CMR imaging is based on the Lake Louise Criteria. CMR is useful to assess left ventricular volume, size and function, the presence of myocardial inflammation/injury, and the evidence of pericardial effusion. As per the 2009 criteria, in the setting of clinically suspected myocarditis, at least two of the following criteria must be present on CMR to support presence of myocardial inflammation: (1) regional or global myocardial signal intensity increase in T2 weighted images (including evidence of myocardial edema with increased septal thickness), (2) increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images (indicating myocardial hyperemia and capillary leak), and (3) at least one focal lesion of myocardial injury with non-ischemic regional distribution on LGE [60]. It is important to note that with the recent modifications to the Lake Louise Criteria in 2018, the myocardial early global gadolinium enhancement ratio has largely fallen out of favor due to the inconsistent image quality of skeletal muscle to be used as a reference point and two of two criteria were required for a diagnosis of acute myocardial inflammation (Figure 4) [62]. Two of two criteria are now required for an MRI diagnosis of acute myocardial inflammation which included (1) myocardial edema (on T2 mapping or T2 weighted images) and (2) non-ischemic myocardial injury (via abnormal T1 mapping, Extracellular volume fraction, or LGE) [63]. Typical findings of myocarditis can be seen in Figure 5. The additional findings of left ventricular systolic dysfunction or pericardial effusion, while not diagnostic, can provide additional supportive evidence for myocarditis.

While CMR was a challenge to obtain in early days of the pandemic, follow-up studies on COVID-19 infected and SARS-CoV-2 mRNA vaccine-associated
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Myocarditis revealed unique characteristics otherwise not seen in other forms of myocarditis (Figure 6). A similar pattern of myocardial injury was seen between vaccine-associated myocarditis compared with other causes of viral myocarditis involving the basal infero-lateral wall. However, COVID-19 myocarditis exhibited more widespread fibrosis patterns, such as subepicardial involvement. Those with vaccine-associated myocarditis had less extensive LGE that spared septal involvement [65]. In addition, patients recovering with post COVID-19 syndrome (54%) commonly have cardiac...
abnormalities: myocardial scar formation (32%), residual pericardial effusion, myocardial edema and interstitial fibrosis likely from persisting inflammation and increased vascular permeability [66].

Five other non-exclusive LGE patterns seen in CMR studies of patients with myocarditis include: (1) subepicardial (common with Parvovirus B19), (2) intramyocardial (common with co-infection of HH6 and PVB19), (3) focal (common mimic of sarcoidosis or neoplasm), (4) transmural (can mimic myocardial infarction), (5) patchy or multifocal (common with co-infection of HH6 and PVB19, or sarcoidosis) [67]. Septal involvement and degree of LGE was found to be associated with worse outcomes and higher rates of major cardiac events, which supports the utility of CMR in prognostication, adding valuable information not only on tissue characterization but risk stratification in patients with suspected myocarditis [68, 69].

CMR is generally appropriate when patients present with (1) new onset or persisting symptoms suggestive of myocarditis (dyspnea, orthopnea, palpitations, exercise intolerance, chest pain), (2) evidence of recent/ongoing myocardial injury (ventricular dysfunction, new or persisting ECG abnormalities, elevated troponin), (3) suspected viral etiology (history of recent systemic viral disease or previous myocarditis). Additional considerations that support a CMR study include the absence of coronary artery disease risk factors, age < 35 years, and symptoms not explained by coronary stenosis on angiogram or a recent negative ischemic stress test [60]. In addition, in patients presenting with new onset heart failure, CMR may be useful in delineating myocarditis from other related or structural abnormalities seen in conditions such as hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathies, left ventricular non-compaction, congenital heart disease with shunt evaluation, or in evaluating other causes of idiopathic dilated cardiomyopathies. This can be of particular importance for the assessment in younger patients with possible vaccine-associated myocarditis who may present with arrhythmias or heart failure and can help guide appropriate management and follow-up, including the return to exercise or competitive sports.

In 2016, the MyoRacer Trial demonstrated the usefulness of mapping techniques in biopsy proven patients with acute symptoms, to confirm or reject myocarditis, superior to the Lake Louise Criteria. In patients with acute symptoms, native (pre-contrast) T1 mapping was a more specific and sensitive test. However, T2 mapping was a superior diagnostic tool in patients with chronic symptoms [70].
In the case of cardiac sarcoidosis and myocarditis, CMR has been shown to improve diagnostic capabilities. In studies, cardiac involvement varies from 0.58 to 7.4%, for clinical diagnosis, which increases from 13 to 45.7% with CMR, and from 24 to 45% on autopsy. Up to 19% of patients had LGE in the absence of cardiac symptoms [71]. Important limitations exist with CMR and specifically LGE. LGE could mimic other nonischemic and ischemic diseases and can be undetectable in healed myocarditis. Falsely larger areas of fibrosis may be present in acute myocarditis where necrosis is in conjunction with edema or absent in mild diffuse disease if separate edema sequences are not performed [72]. Despite the limitations, a subgroup of the ITAMY study investigating the prognostic value of a repeat CMR 6 months after the initial scan demonstrated the greatest survival probabilities in those with complete resolution of edema and LGE, while edema without LGE suggests a residual chance of recovery followed by the worst prognosis in those with residual LGE (especially midwall septal pattern) without edema, likely representing persistent fibrosis [73].

3.4 Biopsy

While the gold standard for diagnosing myocarditis remains histopathological evidence via endomyocardial biopsy (EMB), the invasive nature of the procedure has made the alternative, often a clinical diagnosis (history, examination, labs, ECG)

![Clinical and diagnostic approach to diagnosis of myocarditis.](image-url)
along with echocardiogram and CMR much more common in practice. Biopsy is often reserved in cases of acute myocarditis due to its invasiveness but becomes particularly important in fulminant myocarditis. The initial clinical approach to diagnosis of myocarditis is illustrated in Figure 7. An EMB should be performed in the setting of unexplained acute cardiomyopathy (usually a dilated cardiomyopathy) and when other causes of cardiomyopathy have been excluded (ischemic, hypertensive/valvular, metabolic, toxic) in a patient that demonstrates symptoms of refractory heart failure not responding to guideline directed medical therapy, high grade heart block, symptomatic VT or requiring inotropic or mechanical circulatory support [74]. When there is adequate suspicion for giant cell myocarditis, a rare but important cause of cardiomyopathy, death, and transplant, EMB has shown an 82–85% sensitivity on diagnosis [75]. If diagnosed early, it can respond to calcineurin based treatment (cyclosporine) with positive outcomes on treatment course. In contrast, low-risk patients with more benign clinical presentations (hemodynamic stability, mild to normal LVEF >50%, without ventricular arrhythmias or heart block), CMR is preferred over EMB [49].

EMB has the potential for guiding therapy in patients with myocarditis or inflammatory related cardiomyopathies. These patients can be classified into four groups based on biopsy results (Figure 8): inflammation-negative, virus-negative; inflammation-positive, virus-negative; inflammation-negative, virus-positive; and inflammation-positive, virus-positive. In addition to guideline directed medical therapy for heart failure, immunosuppressive therapy should be a mainstay for virus-negative inflammatory cardiomyopathy [23]. It should be noted the potential relationship between an idiopathic dilated cardiomyopathy and various stages of myocarditis, thus, it is prudent to delineate the presence of residual inflammation or virus in such patients with a thorough investigation albeit myocardial biopsy and/or advanced cardiac imaging, if clinically indicated. In addition, further research is

Figure 8.
Categories of myocarditis based on endomyocardial biopsy results. Adapted from [23].
needed regarding the potential role that autoantibody targeting may have in autoimmune, or virus associated inflammatory heart disease.

4. Management/prognosis

In line with the broad spectrum of etiologies, management of myocarditis includes conventional treatment for arrhythmias and heart failure along current guidelines [49, 76]. Tachy or bradyarrhythmia is common in the acute phase of myocarditis or can be asymptomatic. Antiarrhythmic therapy is generally reserved for symptomatic ventricular tachycardia or supraventricular tachycardias that can exacerbate underlying heart failure. Cardioversion can be considered for sustained ventricular arrhythmias. Implantable cardioverter (ICD) is indicated per guideline directed therapy for life threatening arrhythmias or persistent myocardial dysfunction.

Pharmacological treatment is the most common, first line approach including beta blockers for less than class IV heart failure, or the use of amiodarone, dofetilide in refractory cases. Patients that present with hemodynamic stability with sequelae of either acute or chronic heart failure should receive diuretics, angiotensin-converting-enzyme inhibitors, or angiotensin-receptor blockers and beta-adrenergic blockers if tolerable. Aldosterone antagonists may be added for more advanced heart failure with symptoms that persist or LVEF <35%.

The presentation of hemodynamically unstable heart failure may require mechanical circulatory support. In patients presenting with cardiogenic shock where there is severe ventricular systolic dysfunction refractory to medical therapy, ventricular assist devices or extracorporeal membrane oxygenation (ECMO) may be required to prevent multi-organ dysfunction and provide a bridge to recovery by allowing for myocardial recovery or transplant [77].

Patients with myocarditis are encouraged to avoid nonsteroidal anti-inflammatory drugs, alcohol consumption or other toxin mediated substances that have been shown to increase severity of myocarditis. Abstinence from heavy aerobic physical activity has been shown to reduce myocardial demand and reduce the potential for accelerating viral replication. Avoiding physical activity for a period of 3–6 months following the acute phase of myocarditis is recommended with reassessment every 6 months, including the use of repeat biopsy or advanced imaging such as CMR [49, 78].

Current ACC/AHA/ESC guidelines recommend consideration of immunosuppression for patients with active myocarditis and negative viral genome on EMB. A viral genome analysis is generally recommended on EMB samples to determine the safe use of immunosuppressants. Immunosuppressant regimen combinations that include glucocorticoids, azathioprine, cyclosporine is the basis for therapy for giant-cell myocarditis, cardiac sarcoidosis and eosinophilic myocarditis (once drugs or parasites have been ruled out). Patients with a positive viral biopsy for PVB19, HHV-6, CMV, Epstein-Barr, should have initial treatment with antiviral therapy during the acute phase then maintenance with immunosuppression. Ongoing, future, studies for alternative regimens include: the Myocarditis Therapy with Steroids [MYTHS] trial, Anakinra versus Placebo for the Treatment of Acute Myocarditis [ARAMIS], Abatacept for the Treatment of Immune-Checkpoint Inhibitors Induced Myocarditis [ACHLYS].
5. Conclusion

Myocarditis is a heterogeneous disease ranging from mild, self-limiting to fulminating, including the manifestations of heart failure, cardiogenic shock and/or death. While myocarditis has numerous etiologies, viral myocarditis is the most common. Despite an array of clinical, laboratory biomarkers, imaging and biopsy, there is not one sole diagnostic method for its diagnosis. Laboratory markers may provide clues to its diagnosis and their use for continued surveillance may prove useful to monitor disease severity and response to treatment. Echocardiography is a valuable initial modality for the assessment of left or right ventricular dysfunction and to assess hemodynamic instability or secondary complications of myocarditis. Despite the gold standard method of biopsy, it poses several limitations in invasiveness, the diagnostic accuracy based on the location or degree of cardiac involvement, pathological interpretation and resource limitations, and hence, is reserved in refractory cases or those with hemodynamic instability. CMR has superior utility in evaluating myocarditis non-invasively, not only at its diagnostic stage but also in various sub-clinical or convalescent stages of myocarditis and to ensure adequate resolution and follow-up in such patients. Findings in CMR may also overlap with other dilated or idiopathic cardiomyopathies and may be of particular use in conjunction or independent of biopsy. In the new post COVID-19 era, the utility of CMR provides an excellent modality to delineate various cardiomyopathies where an infectious or inflammatory mediated process is in the differential. Clinicians should ensure a comprehensive work-up and thorough surveillance while caring for such patients.

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Michael R. Sood, MD, MS, FACC, FSCMR is the Director of Cardiovascular Magnetic Resonance at Mount Sinai South Nassau.

Conflict of interest

The authors declare no conflicts of interest.
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