An Overview of the Pathogenesis, Etiologies, and Treatment of Myocarditis

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Disease Overview

Myocarditis is the inflammation of the myocardium typically as a result of infection, due to viruses, bacteria, fungi, or parasites. Other potential, non-infectious etiologies include, the ingestion of medications or toxic substances, autoimmune disorders, or other systemic disorders that trigger inflammation of the heart muscle and can result in the death of cardiomyocytes. Consequently, a variety of complications can arise. Heart enlargement, myocardial weakening, arrhythmias, clot formation, and muscle damage can occur. Damage to the myocardium can be detrimental, in particular, because it results in the formation of scar tissue that is less effective at pumping blood throughout the body. In severe cases, myocarditis can require heart transplantation or can lead to congestive heart failure (CHF), myocardial infarction (MI), or sudden cardiac arrest (SCA).

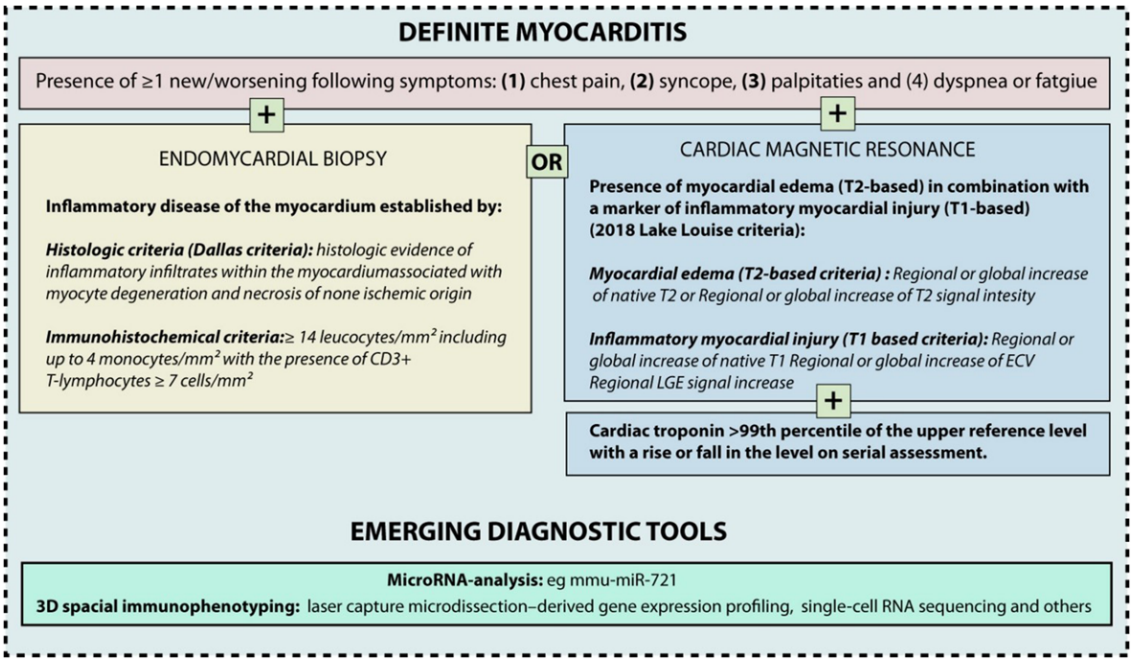
It is reported as one of the most common causes of sudden cardiac death in young adults. Having stated that, it typically afflicts younger adult males; however, women, as well as children, are still shown to develop it but at much lower rates. Signs and symptoms vary across the sexes, age groups, and the myocarditis subtypes. That being said, the most common ones for adults are listed as, chest pain, dyspnea, fatigue, fever, palpitations, tachycardia, tachypnea, syncope, and swelling of the lower extremities (legs, ankles, and feet). Women may present with more subtle signs and symptoms, which can pose a problem for proper diagnosis; meanwhile, signs and symptoms usually go unnoticed in children until the case has become more severe.

Disease progression of myocarditis is most commonly categorized into acute (symptoms lasting less than a month), fulminant (severe form of acute myocarditis, characterized by rapid evolvement), subacute (symptoms lasting from one month to three months), and chronic (symptoms lasting longer than three months).

Diagnostic Methods

Myocarditis is characterized by a diverse clinical presentation, making diagnosis of the condition as a whole challenging. Therefore, the focus of most physicians is to rule out related conditions, such as acute coronary syndromes and acute pericarditis, that have similar clinical features. In most cases, further investigation into the etiology responsible for the myocardial inflammation is not pursued. This is often due to the expenses surrounding additional diagnostic testing, as well as the significant health risks they may pose to the patient. However, physicians may investigate the underlying causes and perform additional tests in severe cases or if patient care could be significantly impacted by subtype classification. Most testing consists of blood tests (to analyze cardiac enzymes), electrocardiograms (ECGs), chest x-rays, cardiac magnetic resonance imaging (CMR), transthoracic echocardiograms (TTEs), and endomyocardial biopsies (EMBs). In recent years, there has also been the emergence of microRNA-analysis, which has the potential to drastically impact the accuracy of myocarditis diagnosis, classification, and patient treatment (Figure 1).

Figure 1.



Common & Emerging Diagnostic Tools for Myocarditis. Image by *JAHA* (2023).

Oftentimes, an ECG is the first test done in patients presenting with cardiac problems. Findings can be typical or atypical for myocarditis patients; however, they will more often than not have an abnormal ECG. In most instances, patients will present with wide QRS patterns, ST segment abnormalities (specifically elevation), prolonged QT, acute myocardial infarction patterns, bradycardia, sinus tachycardia, an atrioventricular block, and/or ventricular arrhythmias [1]. These findings, namely ST segment elevation, are not necessarily specific to myocarditis patients and can be found in cases of pericarditis or myopericarditis. Therefore, an ECG alone is not sufficient enough for a definitive diagnosis.

Physicians will also order blood work, which can provide insight into the etiology. The full blood count is assessed and it may be normal; however, an increased eosinophil count can be indicative of eosinophilic myocarditis. Special attention is typically given to C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and cardiac biomarkers. Studies have found that CRP was raised in over 80% of myocarditis patients and their ESR increased as well [2]. In fact, if ESR remains high over an extended period of time, that can indicate the etiology is autoimmune-related. One of the key cardiac biomarkers that is assessed in suspected myocarditis patients is troponin. Myocarditis is typically characterized by raised troponin levels. Increased troponin levels can be indicative of myocardial necrosis; however, a lack of increased levels does not rule out the possibility of myocarditis. That being said, it is helpful in differentiating myocarditis from pericarditis, as pericarditis is not characterized by elevated troponin. Another cardiac biomarker commonly assessed is serum brain natriuretic peptide (BNP). Again, elevated BNP levels can be indicative of myocarditis, but patients may also present with normal levels.

Significant elevation in troponin and BNP levels may necessitate and expedite the need for further investigation into the underlying causes via CMR or EMB.

TTE is another common part of the diagnostic process for myocarditis. It may be performed to rule out other conditions that also result in heart failure. Findings can range, but they usually include: “reduced left ventricular ejection fraction (LVEF), diastolic dysfunction, increased cardiac wall thickness, segmental wall motion abnormalities, abnormal echogenicity of the myocardium or a pericardial effusion” [2]. Oftentimes, segmental or global wall-motion abnormalities and increased volume in the left ventricle characterizes acute myocarditis; meanwhile, fulminant myocarditis patients may present with a decrease in the size of their left ventricle, along with thickening of their cardiac walls [3].

In recent years, CMR has become the standard non-invasive procedure performed to determine the presence of myocardial inflammation, as well as to assess other cardiac irregularities. Researchers have found that, “regions of myocarditis are reported to correlate closely with regions of abnormal signal on cardiac MRI” [3]. Hence, clinicians have shifted towards this method of diagnosis, especially because it poses significantly less risks compared to EMB. It is typically performed two to three weeks following the onset of symptoms to ensure the highest degree of accuracy, but it can also be used as a means of monitoring disease progression. CMR with “intravenous gadolinium-based contract agents” is recommended in cases of suspected acute myocarditis, and even more so in fulminant cases [2]. CMR can also be used to identify sites for potential EMB extraction.

EMB has long been considered the “gold standard” of diagnostic testing for myocarditis; however, it is severely limited and can pose significant risks. The procedure can be helpful in confirming a diagnosis and potentially deducing the aetiopathogenic origins of the disease. That being said, it is an invasive procedure done via a transfemoral or transradial approach. The risks associated with it include: arrhythmias, pneumothoraxes, and post-procedure infections. These complications are less likely to occur when the procedure is performed by experienced teams, with a risk of complication estimated at 1-2%. However, in low volume settings the risk of complication can be up to 9% [2]. It is worth noting that not all patients are suitable for EMB. Additionally, due to the patchy nature of myocarditis, a biopsy may be non-diagnostic if the sampled tissue was not affected. Consequently, a large number of tissue samples may need to be collected in order to make an accurate diagnosis; however, this is often not feasible in a clinical setting, as discussed later. Consequently, the rate of EMB has decreased over the last few decades, being performed in 3% of all acute myocarditis cases [4]. Most physicians have reached the consensus that EMB should be reserved for “finding specific treatable disorders” and in cases where patient management may be drastically affected [3].

There are a range of additional diagnostic tests that may be performed in suspected myocarditis patients; however, those investigations lie beyond the scope of this review.

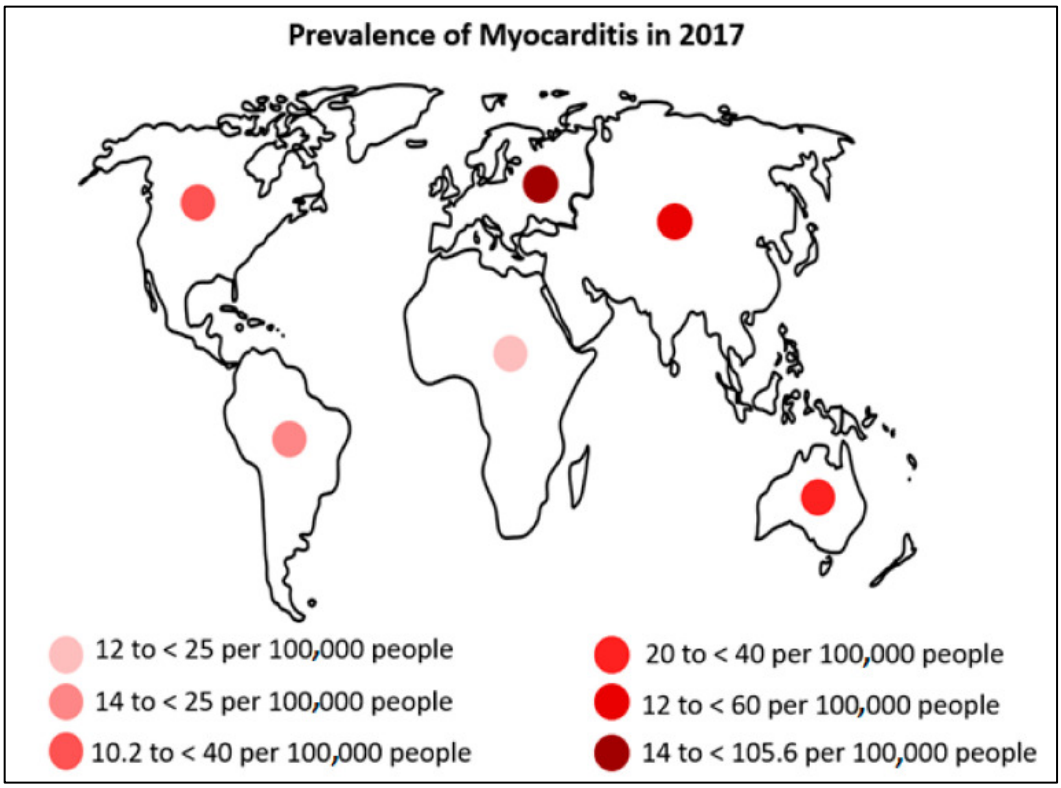
Epidemiology

Up until recent years, myocarditis was classified as a rare condition; however, new research indicates that its prevalence is likely greater than reports claim. As of now, its global prevalence is estimated at 10.2 (in Chile) to 105.6 (in Albania) per 100,000 with an incidence of approximately 1.8 million on an annual basis, according to data collected in 2017 [5]. As these numbers demonstrate, the exact prevalence of myocarditis is challenging to determine and the underdiagnosis of this condition, for various reasons, is believed to contribute to the uncertainty surrounding the true number of myocarditis cases worldwide. In 2017, an estimated 46,486 people around the world died from myocarditis. Mortality rates differed between countries by a factor of 43.9 and the aforementioned prevalence rates differed by a factor of 10.4 [5]. It is reported that from 1990 to 2017, there was a decrease in age-standardized rates; however, there has been a marked increase in both prevalence and death rates in recent years.

As previously discussed, myocarditis has a broad range of symptoms that often mimic those present in other heart conditions like coronary artery disease, CHF, pericarditis, and various cardiomyopathies. Consequently, these similarities between disease presentation, in conjunction with pitfalls in diagnostic testing, may be partially responsible for the underreporting of myocarditis incidences. As discovered in 1989, the EMBs performed required roughly 17 specimens from the right ventricle to detect myocarditis in 79% of cases [5]. The collection of such a high number of tissue samples is not feasible when conducting biopsies, and is therefore not standard procedure. Consequently, standard biopsy testing for myocarditis likely achieves a low sensitivity of detection, meaning that false negatives may often be reported which contributes to the underdiagnosis of myocarditis. That being said, there are other factors, such as the nature of the disease itself, that pose challenges to accurate diagnosis estimations. The patchy nature of myocarditis means that inflammation/damage is only present in certain areas. Consequently, a large number of EMB samples may have to be obtained for diagnosis. Estimations are further limited by the lack of EMBs performed, which is considered the most reliable diagnostic tool, due the invasiveness of the procedure. Considering this information, it is difficult to account for the exact prevalence of myocarditis.

Incidence cases demonstrate that there are sex-specific differences in myocarditis. A significant percentage of myocarditis patients are men; they accounted for approximately 82% of myocarditis cases in 2017 [5]. Additionally, these male patients were more likely to develop more severe forms of myocarditis that lead to an increased risk of death or the need for a heart transplant. That being said, it is possible that women are underdiagnosed with myocarditis due to the subtlety that characterizes their signs/symptoms. Beyond this, increased male affliction was believed to be due to differences in the innate immune response to Coxsackievirus B3 (CVB3) between the sexes. It is also worth noting that these men were typically young adults, ranging from late teens to mid-twenties; however, older men can still be afflicted, though it is less common.

Figure 2.



Global prevalence of Myocarditis in 2017. Image by *Journal of Clinical Medicine* (2021).

Studies also show regional differences in myocarditis prevalence. The highest prevalence of myocarditis was reported in wealthier areas of the Asia-Pacific region (45.6 per 100,000 individuals), with the highest death rate localized to Oceania (2.6 per 100,000 individuals). Researchers claim this high death rate could be due to a lack of medical resources throughout the region, but beyond this the cause remains unclear. Prevalence of the various myocarditis subtypes, along with their specific etiologies, varies significantly from region to region. Furthermore, studies demonstrate a shift over time in the viruses, infections, or toxins responsible for inducing myocarditis.

From 1966 to 2000, diphtheria, typhoid fever, CVB3, Chikungunya, and hepatitis C virus were the most common infectious causes for myocarditis in Asia. Diphtheria was especially prominent in India and Afghanistan; meanwhile, hepatitis C virus was prevalent in Japan and was found to be a causative agent in a significant number of cardiomyopathies. In Australia and New Zealand, infectious myocarditis has shown to be due to CVB3, as well as enterovirus 71. Studies indicate that human immunodeficiency virus (HIV), trypanosomiasis, and shigellosis are the most frequent causes of myocarditis in African countries.

Chagas Disease (CD), caused by the parasite *Trypanosoma cruzi*, is one of the primary causes for myocarditis in Latin America. Of the EMBs taken from patients infected with *T. cruzi*, approximately 60% of them presented with inflammation of the myocardium. CD must be

considered globally, not only in areas in which it is endemic. This is due to the migration of individuals from CD endemic areas in Latin America to other countries like Spain, Italy, France, Switzerland, and the United Kingdom. In 2009, there were 4,290 CD cases reported in Europe; however, researchers estimated that there were likely 63,318 to 123,078 people infected with *T. cruzi* across Europe [5]. This not only indicates a severe underdiagnosis of CD (by roughly 94-96%), but reaffirms the need for consideration of CD as a causative agent for myocarditis worldwide. Beyond CD, infectious myocarditis cases in Mexico, Central America, and South America were caused by measles, meningococcal meningitis, HIV, dengue, and diphtheria.

Data on toxic myocarditis prevalence around the world is limited. That being said, studies indicate that clozapine, anabolic steroids, and smallpox vaccines (although incredibly rare) were possible causes of toxic myocarditis in New Zealand and Australia. Excessive alcohol consumption is another potential cause of toxic myocarditis, as proven by EMBs taken from patient populations. Alcohol-induced cardiomyopathies reportedly impact 1.54 billion people globally, with a high percentage residing in the United States, as well as European nations [5]. Toxic myocarditis has also been reported in various regions of India, but unlike other countries, its cause is more unique. Scorpions native to India, specifically the *Mesobuthus tamulus* and *Heterometrus swammerdami* species, have been shown to induce toxic myocarditis (adrenergic myocarditis); figures regarding the prevalence of such exposure remain unreported.

Subtypes and Etiologies

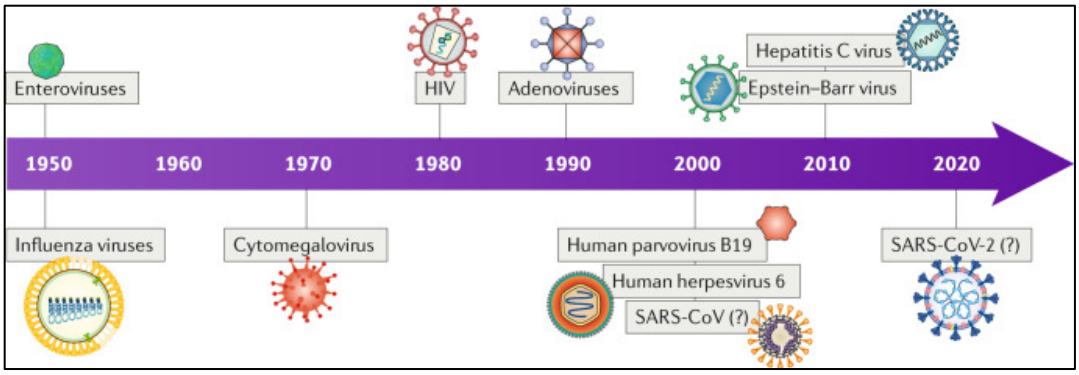
The etiologies of myocarditis are vast and much remains to be discovered. With this in mind, classifying myocarditis into distinct categories can be a challenge, especially due to the interplay between causative agents; however, it can be generally classified into infectious or non-infectious origin. A variety of microorganisms can act as infectious agents and cause inflammation of the myocardium. These pathogens include, viruses, bacteria, protozoa, parasites, fungi, and helminths. Within the non-infectious category, there are many causes including, but not limited to: autoimmune diseases, toxic or hypersensitivity reactions to drugs or toxins, and systemic disorders like sarcoidosis. It should be noted that giant-cell myocarditis and cardiac sarcoidosis-induced myocarditis are considered idiopathic conditions and they are comparatively rare subtypes.

Infectious

Epidemiological findings indicate that viruses are the primary cause for myocarditis worldwide. These viruses can be classified as cardiotropic, lymphotropic, vasculotropic, cardiotoxic, or Angiotensin-converting enzyme 2-tropic (ACE2-tropic). From the 1950s to the 1990s, CVB3 was often implicated in myocarditis, after which it switched to adenoviruses as the main culprit. Within the last decade, it has shifted to parvovirus B-19 and human herpesvirus 6 as the predominant causative viruses in North America and Europe. Other viruses, less commonly associated with myocarditis include, Epstein–Barr virus, cytomegalovirus, enteroviruses, HIV, and hepatitis C virus. As previously discussed, the prevalence of these viruses varies from region

to region and data can be conflicting at times. HIV, in particular, is a significant causative agent; however, it is less prevalent in the United States. It is a common cause of myocardial injury in lower income nations and reports demonstrate that myocarditis was present in over 50% of HIV patients with cardiomyopathies [3]. In a similar manner, hepatitis C infection was connected to myocarditis and other cardiomyopathies in Japan; however, this is significantly less frequent in the US.

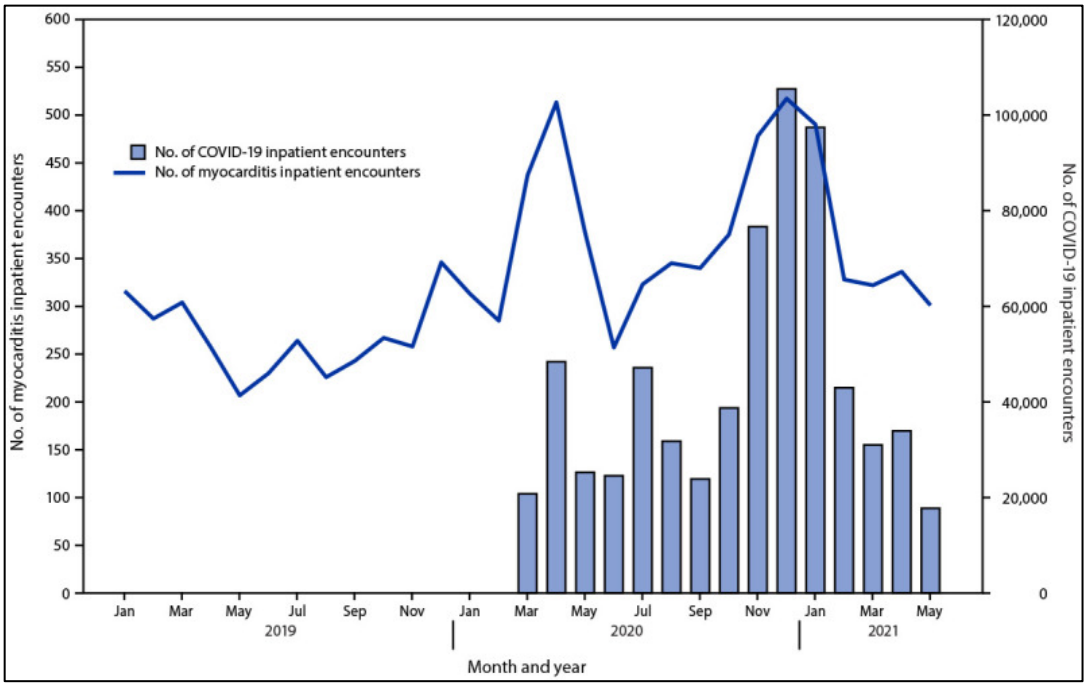
Figure 3.



Timeline for predominant viruses related to inflammatory cardiomyopathies. Image by *Nature Reviews Cardiology* (2021).

In recent years, there has been a greater focus on the association between myocarditis and SARS-CoV-2, the virus that results in COVID-19 (Figure 3). The available data indicates that direct myocardial damage due to SARS-CoV-2 is uncommon in most patients; however, a survey conducted by the CDC in US hospitals from March 2020 to January 2021 showed that infected patients were nearly 16 times more at risk for developing myocarditis compared to those that were uninfected [6]. Furthermore, “the number of myocarditis inpatient encounters (4,560) [in 2020] was 42.3% higher than that during 2019 (3,205)” [6]. The accumulated data demonstrated that these spikes in myocarditis inpatient encounters typically coincided with an increased number of COVID-19 cases, particularly between November 2020-January 2021 (Figure 4). Additionally, researchers within this study found that roughly 40% of the patients diagnosed with myocarditis had been previously diagnosed with COVID-19. It should be noted that COVID-19 patients with myocarditis tended to be older (median age of 54) and they were typically male (59.3%) [6]. That being said, it appeared that infected children, 16 years old and younger, also had a higher risk of developing myocarditis as well. Considering the data collected in this study, there is evidence for an association between myocarditis and SARS-CoV-2 infection; however, this does not prove that a causative relationship exists. Other major studies conducted in the US and in Israel during 2020-2021 also demonstrated this association. Despite the available data, much more remains to be discovered about the connection between COVID-19 and myocarditis, along with its proposed pathogenesis.

Figure 4.



Recordings of COVID-19 and myocarditis inpatient encounters from 2019 to 2021. Image by *MMWR* (2021).

Bacteria also act as significant infectious agents for cardiomyopathies. Some bacterial agents include, *Corynebacterium diphtheria*, *Beta-haemolytic streptococci*, *Borrelia burgdorferi, Meningococci*, *Salmonella typhior paratyphi*, *Mycoplasma pneumonia*, *Chlamydia psittaci*, and *Corynebacterium diphtheria*. Of note are *C. diphtheria, B. burgdorferi,* and *Beta-haemolytic streptococcus*. Myocarditis, induced by these various types of bacteria, is significantly less common in Western regions of the world; however, *C. diphtheria* poses a significant threat in less developed nations. With this in mind, there are some researchers that claim *C. diphtheria* infection may actually be the most common global cause of myocarditis. Another noteworthy bacterium is *B. burgdorferi,* which results in Lyme disease. This bacterial infection can result in a specific form of myocarditis, termed Lyme myocarditis, which evidently appears more in areas where Lyme disease is endemic. Finally, *Beta-haemolytic streptococcus*, the bacterium that causes rheumatic fever, has been implicated as a leading cause of cardiac-related hospitalizations among those aged five to twenty-five in underdeveloped regions. Beyond bacteria, protozoa appear to act as causative agents as well. In Central and South America, the protozoan, *T. cruzi*, can result in infection and said infection can present itself as either acute myocarditis or other more chronic cardiomyopathies.

Toxic/Hypersensitivity/Eosinophilic

Toxic myocarditis, also labeled hypersensitivity myocarditis, is myocardial inflammation resulting from toxic exposure or a hypersensitivity/eosinophilic reaction to drugs or vaccines. A range of prescribed medications, such as dobutamine, phenytoin, ampicillin, azithromycin,

cephalosporins, tetracyclines, tricyclic antidepressants, benzodiazepines, and clozapine have been shown to trigger toxic myocarditis. That being said, illicit drugs, namely methamphetamine or cocaine, heavy metals, and antineoplastic agents have also been implicated as causative agents.

In the 1950s to 1960s, the smallpox vaccine resulted in a small number of myocarditis cases, which were believed to have been hypersensitivity reactions to the vaccine. These reactions were reportedly strain dependent. It is estimated that the incidence of myocarditis at the time equated to roughly 0.01%; however, the exact numbers remain unknown [5].

In recent years, there has been a greater emphasis on exploring the connection between vaccination-induced hypersensitivity reactions and myocardial inflammation, especially in light of the COVID-19 pandemic. Studies conducted by both the CDC and the Israeli Ministry of Health found that mRNA COVID-19 vaccine recipients, specifically males between the ages of 12 to 29, had an increased risk of developing hypersensitivity myocarditis. There were approximately 39-47 cases per million upon administration with a second dose [6]. Similarly, Barda and colleagues found an increased risk of myocarditis upon vaccination, based upon data from Israel's largest healthcare organization, Clalit Healthcare Services. They determined that the risk of developing myocarditis increased threefold following the administration of the mRNA COVID-19 vaccine. Furthermore, they identified that younger males in particular had an increased risk of myocarditis development: "Among the 21 persons with myocarditis in the vaccinated group, the median age was 25 years (interquartile range, 20 to 34), and 90.9% were male" [7]. That being said, the Advisory Committee on Immunization Practices still recommended COVID-19 vaccination despite the associated risks, due to the risks associated with SARS-CoV-2 infection that are not associated with the vaccine. The potential risks include, arrhythmia, pulmonary embolism, acute kidney damage, deep-vein thrombosis, and intracranial hemorrhage. There are also risks, beyond myocarditis development, associated with the mRNA COVID-19 vaccine, particularly Bell's palsy and thromboembolic events; however, these are beyond the scope of this discussion.

Iron overload (hemochromatosis) is also a suspected cause of toxic myocarditis. It is believed that excessive iron retention causes the deposition of iron within the myocardium. This can lead to a variety of injuries, namely ventricular enlargement and dysfunction, which can result in heart failure. That being said, research has yet to prove whether or not there is a causational relationship between hemochromatosis and myocardial inflammation.

As previously mentioned, exposure to various toxins can also result in toxic myocarditis. One such example can be seen in the aforementioned scorpion species, the *Mesobuthus tamulus* and *Heterometrus swammerdami* species. These species that are native to specific regions of India release life-threatening venom upon stinging that have been shown to induce toxic myocarditis. The venom produced by these scorpions contains a variety of toxins, namely iberiotoxin and hetlaxin. Investigations into the activity of these toxins have shown that they stimulate the

release of epinephrine and norepinephrine at various sites throughout the central nervous system. This results in decreased Na-K-ATPase and an increased myocardial oxygen demand; ultimately, culminating in adrenergic myocarditis, a subtype of toxic myocarditis.

In eosinophilic myocarditis, a range of systemic inflammatory disorders such as hypereosinophilic syndrome, the Churg–Strauss syndrome, Löffler's endomyocardial fibrosis, cancer, systemic lupus erythematosus, Graves' disease, diabetes mellitus, inflammatory bowel disease, and granulomatosis with polyangiitis can potentially be responsible for myocardial inflammation. This subtype is characterized by the increased accumulation of eosinophils within the myocardium, resulting in inflammation. The fact that an estimated 7% of myocarditis patients have one of the associated autoimmune/inflammatory conditions listed above, necessitates the pursuit of research exploring the connection between autoimmune dysregulation and myocarditis development [8].

Granulomatous

For many years, giant-cell myocarditis (GCM) and cardiac sarcoidosis (CS) were considered different phenotypes of the same disease. Thus, they were collectively classified as granulomatous myocarditis. In recent years there has been a shift towards labeling them as distinct diseases considering the variation in their disease formation; however, some researchers maintain that they are merely distinct phenotypes of the same condition.

GCM is considered one of the rarest forms of myocarditis. It typically takes on a fulminant course, making it one of the most lethal subtypes with a median survival of 3 months without treatment. Oftentimes, patients with go into cardiogenic shock or present with heart blocks and ventricular arrhythmias. It is responsible for an estimated 17% of myocarditis deaths [9]. Unfortunately, much remains unknown its etiologies and mechanisms of action; however, it is believed to have a connection to autoimmune regulation. More specifically, it is theorized that T-lymphocytes and giant-cells invade the myocardium, resulting in fibrosis which culminates in the aforementioned fatal arrhythmias and systolic dysfunction.

CS is also characterized by myocardial injury resulting from T-lymphocyte action; however, there is a notable presence of granulomas in CS that is often absent in GCM. Furthermore, CS patients typically has a better prognosis and less aggressive course compared to GCM patients. CS patients were shown to have a decreased percentage of heart failures (20% prevalence comparted to 46%) and an increased one year survival percentage (82% comparted to 45%) [10]. Despite these differences, the similarities in their clinical and histopathological characteristics complicates differentiation between the two diseases and the raises the question on whether they can truly be considered distinct.

Pathogenesis

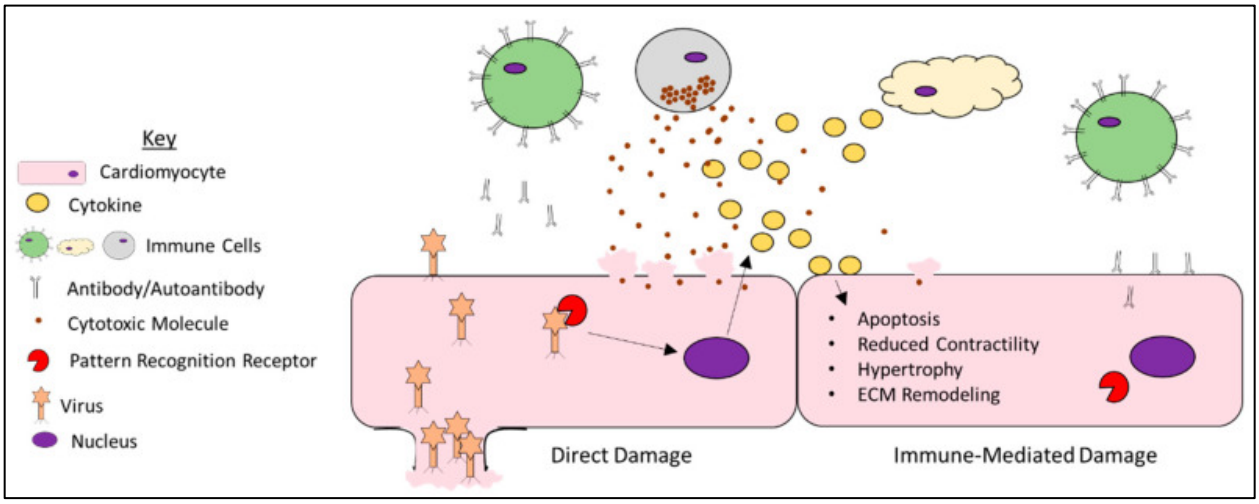
As previously mentioned, the processes by which myocarditis develops, along with the mechanisms of action involved, are not fully understood for all of the subtypes. This is especially

true for cardiac sarcoidosis-induced myocarditis and GCM, for which there is a severe lack of information. That being said, researchers have ascertained the mechanisms of action for an extensive number of viral agents often implicated in myocarditis development. The same can be said for the role the body's own immune cells play in inflammatory cardiopathies, like eosinophilic myocarditis. In the last few years, new theories concerning the mechanisms by which the mRNA COVID-19 vaccine triggers myocarditis have emerged, raising questions regarding the interplay between catecholaminergic activity and androgen levels.

Viral Myocarditis

The mechanisms of damage vary depending on the given virus; however, there are overarching similarities among them. Oftentimes, they will have a direct or an indirect mechanism of action (Figure 5). More often than not, most cardiotropic viruses will participate in both routes of myocardial injury. In direct damage, the virus infects cardiomyocytes, cardiac endothelial cells, and/or fibroblasts, which triggers the overproduction of pro-inflammatory cytokines; ultimately, resulting in damage to the myocardium. Indirect routes of myocarditis development typically involve immune system suppression. Thus, the virus itself may not cause infection directly, but its action weakens the host and makes them more susceptible to other infectious agents.

Figure 5.



Direct versus indirect myocardial damage. Image by *Viruses* (2021).

As discussed above, enteroviruses are common infectious agents that result in myocarditis, with CVB being the most well-researched of them all. CVB-induced myocarditis have courses that vary from patient to patient with some making a full recovery and others having a less favorable prognosis. Unfortunately, this variation remains unclear but the mechanisms of damage by which CVB acts are highly researched. Coxsackieviruses first bind to the surface of cardiac cells via two different co-receptors (decay-accelerating factor and coxsackievirus/adenovirus receptor). After which, these receptors with viruses bound to them are internalized. Translation, using positive sense single-stranded RNA, follows resulting in the synthesis of a polyprotein that is

then used to generate a variety of proteins with different functions. In this process, the host's immune system is weakened due to viral proteases that cleave host factors and mitochondrial antiviral signaling protein. Consequently, interferon (IFN) synthesis, specifically of Type I IFNs, is inhibited. Additionally, CVB infection results in decreased protein release, disrupted calcium signaling, and impaired sarcoplasmic reticulum functioning. Combined, these effects prevent immune cell recruitment and cause dysregulated contractility of the heart, culminating in cardiac injury. Issues can also arise when it comes to the host cell response to CVB infection. Host cells will identify the RNA of CVB via PRRs and then through this pathway, pro-inflammatory cytokine production is stimulated. These cytokines, namely interleukin 1α (IL-1α), IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and IFNγ signal macrophages and natural killer cells to arrive at the area of infection [11]. Following this, T-cells are recruited, indicating the shift from the less specific innate response to the more specific adaptive response. This host response is crucial to prevent the aforementioned direct damage CVB can induce; however, the host's own immune cells can potentially result in cardiac damage, specifically heart failure, by targeting non-infected cells or cardiac myosin.

Herpesviruses, which are DNA viruses, are also often seen in viral myocarditis patients. Human herpesvirus 6 (HHV-6) has been found to infect endothelial cells within the heart, triggering cytokine production which leads to inflammation. Additionally, it has immunosuppressive effects, making the host vulnerable to infection by other viruses that can result in direct injury. Cytomegalovirus (CMV) also has direct and indirect mechanisms of action like HHV-6. Murine studies demonstrated that CMV resulted in the infection of cardiomyocytes, fibroblasts, and endothelial cells. Necrosis was specifically observed in the cardiomyocytes. CMV infection also triggered the upregulation of various cytokines (TNF-α, IL-6, and INFγ), as well as the recruitment of T-cells, which were found to be critical in myocarditis progression. Unlike HHV-6 and CMV, Epstein–Barr virus and Varicella-zoster virus do not have well understood mechanisms of damage.

Similarly to herpesviruses, parvoviruses are also DNA viruses with some shared mechanisms as well. Parvovirus B-19, one of the predominant causative viruses for myocarditis in the last decade, is shown to infect cardiac endothelial cells and then stimulate apoptosis within them. Additionally, it upregulates cytokines and induces autoantibodies.

HIV, a retrovirus, is yet another virus commonly implicated in viral myocarditis. It causes direct damage via infection and apoptosis of cardiomyocytes, along with endothelial cells; however, its indirect mechanisms are considered far more significant in myocarditis development. Like many of the previously mentioned viruses, HIV induces cytokine production following infection which leads to the accumulation of HIV-infected lymphocytes and macrophages in the myocardium. HIV also causes immunosuppression, atherosclerosis, and nutrient deficiency, resulting in cardiac damage.

Finally, influenza viruses and coronaviruses both appear to have direct and indirect mechanisms. These virus families cause direct damage to cardiomyocytes; however, influenza viruses also induce immune-mediated damage. Meanwhile, coronaviruses lead to cytokine overexpression.

Eosinophilic Myocarditis

Researchers believe there are potentially four different mechanisms by which eosinophils cause damage to the myocardium and result in heart failure. The first being, direct damage by eosinophils. Studies indicate that there may be a correlation between the number of degraded eosinophils and cardiac injury. That being said, the most common mechanism of damage appears to be the release of various toxic substances by eosinophils. Research indicates that interleukin-5 triggers the process of degranulation in eosinophils, causing the release of cytotoxic proteins like major basic protein (MBP) and eosinophil cationic protein (ECP). MBP can then result in a variety of different issues within the myocardium. It can potentially disrupt the cell membrane, resulting in increased cell membrane permeability, and it can inhibit cellular respiration within the mitochondria. Consequently, necrosis of, or injury to, cardiac cells can occur. ECP is also cardiotoxic and can lead to problems that eventually culminate in the death of cardiac tissue. In animal studies, ECP was found to initiate the release of histamine and tryptase from mast cells within the heart [12]. A large collection of endomyocardial biopsies taken from myocarditis patients demonstrated higher levels of MBP, ECP, and eosinophil degradation in areas where necrosis and thrombosis occurred; thus, proving their pathogenic role in myocarditis development. The third mechanism by which eosinophilic myocarditis can occur is through eosinophil activation of the coagulation cascade. In triggering this clotting mechanism, eosinophils can potentially cause thrombus development. This will eventually lead to oxygen deprivation to cardiac tissue and the death of myocardial cells. The last mechanism has yet to be proven with sufficient evidence. However, it is theorized that eosinophils can activate the immune system in the same manner as autoimmune disorders: “Persistent infection and inflammation may be responsible for releasing autoantigens from the heart that were previously hidden from the immune system” [12]. These changes in immune system activity can then cause downstream effects within the “microenvironment” of the myocardium that then induces eosinophil degranulation (leading to the aforementioned cardiac injuries).

mRNA vaccine-induced Myocarditis

SARS-CoV-2 mRNA vaccine-induced myocarditis is a rare condition and does not occur in most vaccine recipients. However, multiple research groups across the US identified that a select population, young male athletes, were disproportionately affected by this condition and succumbed to sudden cardiac death in a number of cases. Causality behind this phenomenon has yet to be established. That being said, there is strong evidence to suggest that catecholamines and the production of a hypercatecholaminergic state within the myocardium results in myocarditis and culminates in sudden cardiac death. The following proposed mechanisms of action presented

by Cadegiani are based upon epidemiological data, pathological and molecular findings derived from autopsies, and established physiological pathways.

As previously discussed, epidemiological findings demonstrate that young males, particularly those aged 18-29, are significantly more at risk of developing COVID-19 mRNA vaccine-induced myocarditis. It was reported that these young men had a 3 to 30-fold increased risk of developing myocarditis following mRNA vaccination [13]. Furthermore, in recent years there have been an increased number of sudden cardiac deaths in young male athletes, with a notable increase in 2021.

Autopsies taken from myocarditis patients following vaccine administration revealed a number of patterns in myocardial damage, as well as the accumulation of particular proteins. Autopsies taken from two young myocarditis patients, following BNT162b2 vaccination, found contraction band necrosis (CBN) throughout the myocardium, along with the presence of sarcomeres in a hypercontracted state. Another autopsy, of a 22-year old male that died from myocarditis days following BNT162b2 vaccination, revealed similar patterns of damage. CBN was also present throughout the myocardium, particularly in the left ventricle, as was inflammatory filtrate. This particular pattern of injury, seen across all three cases, is “consistent with stress cardiomyopathy with contraction bands caused by excessive catecholaminergic activity” [13]. Considering this type of damage is specific to increased catecholaminergic activity, Cardegiani claims these autopsies support the notion that a hyperadrenergic state is the connection between myocarditis and sudden death following mRNA vaccination.

Autopsies from myocarditis patients following mRNA vaccination, have revealed an increased accumulation of SARS-CoV-2 mRNA and SARS-CoV-2 spike protein overproduction within the chromaffin cells found in the adrenal medulla. These physiological changes can lead to a range of negative consequences and can potentially provide insight into the pathogenesis underlying this condition. To begin, the accumulation of SARS-CoV-2 mRNA alone can potentially result in a catecholamine storm that damages the myocardium. Additionally, increased spike protein production can lead to issues. SARS-CoV-2 spike protein causes the overexpression of dihydroxyphenylalanine (DOPA) decarboxylase, the enzyme that converts DOPA into dopamine. Consequently, an increased amount of dopamine is made which then triggers the increased production of epinephrine and norepinephrine. Therefore, it appears that the mRNA vaccine, through various actions, contributes to an increased level of catecholamines within the body and creates a hypercatecholaminergic state.

Studies have shown that males naturally have higher levels of catecholamine release, particularly within cardiomyocytes, and have increased responsivity in their beta-2 adrenergic receptors compared to females. Furthermore, data analyses between male athletes and non-athletes, showed that athletes had significantly higher concentrations of catecholamines, even in a rested state. Athletes also presented with higher testosterone levels. Research indicates that high testosterone and high catecholamine levels may act synergistically to promote increased

catecholaminergic activity. Considering this information, Cadegiani hypothesizes that this specific population of people, characterized by increased catecholaminergic activity, may have presented with an increased risk of mRNA vaccine-induced myocarditis and sudden cardiac death because a hypercatecholaminergic state was further induced upon mRNA vaccination.

Treatment and Prevention

Myocarditis treatment typically involves general supportive care and symptom management; however, it can be directed towards a specific pathogenic mechanism if the underlying disorder is known. Additionally, treatment can vary depending upon the disease stage being experienced by the patient.

For patients that present with heart failure or left ventricular dysfunction, an assortment of different therapeutics are typically provided including, ACE inhibitors (enalapril, lisinopril, and ramipril), beta-blockers (metoprolol, bisoprolol and carvedilol), angiotensin receptor blockers, loop diuretics, nitrates, and aldosterone receptor blockers. It should be noted that antiarrhythmics, such as beta-blockers, are prescribed with due consideration. They can negatively impact inotropy and thus exacerbate heart failure; however, they may be given if patients present with atrial or ventricular arrhythmias. For cases in which conditions worsen despite optimal care, or if fulminant heart failure is present, then ventricular assist devices, extracorporeal membrane oxygenation, intra-aortic balloon pump, or transplantation may be the next course of action. Additionally, patients experiencing complete heart block or symptomatic bradycardia may require a temporary pacemaker. If the ventricular arrhythmia persists, then amiodarone administration and an implantable cardioverter–defibrillator may be necessary.

In the treatment of viral myocarditis, administration of the most effective drug therapy can be a challenge due to the diversity of viral agents. Furthermore, the disease stage must also be taken into consideration, as it will determine the available treatment options. In early stages, viral replication is occurring and the infection is considered active. Therefore, it is best to supply patients with antivirals or immunostimulants. In the case of myocarditis caused by herpesviruses, antivirals like artesunate, ganciclovir, and valganciclovir are typically given. Meanwhile, if the infectious agent is an enterovirus, then patients may be prescribed with an immunostimulant, namely interferon-β (IFN-β). It is worth noting that, “most patients with acute myocarditis are diagnosed weeks after viral infection, it is unlikely that antiviral therapy would be provided early enough to be of benefit in acute viral myocarditis” [3]. With this in mind, physicians may choose to forego the administration of antivirals and go directly into prescribing anti-inflammatory drugs; however, if the patient was still in the early stage of viral myocarditis, then immunosuppressive therapy would be very detrimental. In the late stages, past the point of viral replication, most damage is facilitated by the immune system. Therefore, anti-inflammatory medication is typically given, and immunostimulants are avoided. Prednisone, in particular, is an anti-inflammatory drug that has shown to be beneficial in virus-negative individuals.

Immunosuppressive therapy has also proven effective in the treatment of other subtypes, such as giant-cell, CS-induced, and eosinophilic myocarditis. As previously discussed, most cases of GCM are fatal. That being said, a combination of prednisone and azathioprine are typically prescribed as a life-long therapy, in the hope of providing enough time for transplantation to occur. For CS-induced myocarditis patients, corticoid therapy is given alone or can be given in conjunction with immunosuppressants, like azathioprine or cyclosporine. A range of immunosuppressive therapies can be given for eosinophilic myocarditis. Glucocorticoids, cyclophosphamide, methotrexate, azathioprine, or prednisone may be given; however, if none of these treatments work then mepolizumab, hydroxyurea, interferon-α, Imatinib mesylate or anticoagulants may be prescribed, with the last three being experimental treatments [14].

Beyond treatments, there are multiple precautions myocarditis patients should take especially in the early months following diagnosis. It is recommended that patients avoid non-steroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen and indomethacin, along with cardiotoxic drugs. According to international guidelines, a 6 month period of limited physical activity is also recommended following diagnosis. This is includes exercise, along with other forms of physical stress. Once inflammation disappears (confirmed via MRI) and cardiac function has returned to normal, then normal activity can be resumed; otherwise, restrictions may remain in place. There are a number of general preventative measures that patients can take to reduce potential risk such as: reduce sodium intake, limit alcohol consumption, reduce exposure to toxins, practice good hygiene to avoid infection, avoid certain medications linked to myocarditis, and practice safe sex.

Conclusion

Myocarditis is a unique condition with a diverse clinical presentation. It is typically characterized by symptoms like chest pain, dyspnea, palpitations, and tachycardia. Diagnosis can be challenging due to the similarities between it and other cardiomyopathies; however, there are a range of different tests that aid in making a differential diagnosis. Over the years, testing has changed with a significant reduction in the number of EMBs performed. Studies indicate that myocarditis affects a small percentage of the world population with roughly 1.8 million new cases every year. Men appear to be disproportionately affected compared to women; however, there is a potential underreporting of the condition in women, and in general. Viruses are the most common global cause. That being said, there are a number of other infectious agents responsible for inducing myocarditis like, bacteria, fungi, and protozoa. Additionally, a range of non-infectious agents have been linked to myocardial inflammation: medications, alcohol, vaccines, and toxins. The mechanisms of action by which these agents operate are extensive and distinct. That said, they usually involve cytokine overproduction which culminates in inflammation and damage to the myocardium. Oftentimes, physicians focus on providing patients with general supportive care and medications that aid in symptom management. Care can be more specialized if the etiology is known, but that is often not explored in most cases.

There are a number of general preventative measures patients can take to reduce their risk of developing myocarditis again with most of them being lifestyle changes.

References

1. Kang M, Chippa V, An J. Viral Myocarditis. [Updated 2023 Nov 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459259/
2. Lampejo, T., Durkin, S. M., Bhatt, N., & Guttmann, O. (2021). Acute myocarditis: aetiology, diagnosis and management. *Clinical medicine (London, England)*, *21*(5), e505–e510. https://doi.org/10.7861/clinmed.2021-0121
3. Cooper L. T., Jr (2009). Myocarditis. *The New England journal of medicine*, *360*(15), 1526–1538. https://doi.org/10.1056/NEJMra0800028
4. Ferreira, V. M., Schulz-Menger, J., Holmvang, G., Kramer, C. M., Carbone, I., Sechtem, U., Kindermann, I., Gutberlet, M., Cooper, L. T., Liu, P., & Friedrich, M. G. (2018). Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *Journal of the American College of Cardiology*, *72*(24), 3158–3176. https://doi.org/10.1016/j.jacc.2018.09.072
5. Golpour, A., Patriki, D., Hanson, P. J., McManus, B., & Heidecker, B. (2021). Epidemiological Impact of Myocarditis. *Journal of clinical medicine*, *10*(4), 603. https://doi.org/10.3390/jcm10040603
6. Boehmer, T. K., Kompaniyets, L., Lavery, A. M., Hsu, J., Ko, J. Y., Yusuf, H., Romano, S. D., Gundlapalli, A. V., Oster, M. E., & Harris, A. M. (2021). Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data - United States, March 2020-January 2021. *MMWR. Morbidity and mortality weekly report*, *70*(35), 1228–1232. https://doi.org/10.15585/mmwr.mm7035e5
7. Barda, N., Dagan, N., Ben-Shlomo, Y., Kepten, E., Waxman, J., Ohana, R., Hernán, M. A., Lipsitch, M., Kohane, I., Netzer, D., Reis, B. Y., & Balicer, R. D. (2021). Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *The New England journal of medicine*, *385*(12), 1078–1090. https://doi.org/10.1056/NEJMoa2110475
8. Zhong, Z., Yang, Z., Peng, Y., Wang, L., & Yuan, X. (2021). Diagnosis and treatment of eosinophilic myocarditis. *Journal of translational autoimmunity*, *4*, 100118. https://doi.org/10.1016/j.jtauto.2021.100118
9. Gadela, N. V., Krishnan, A. M., Mukarram, O., & Sthalekar, N. (2021). Giant cell myocarditis. *Proceedings (Baylor University. Medical Center)*, *34*(3), 401–402. https://doi.org/10.1080/08998280.2021.1874775
10. Ekström, K., Räisänen-Sokolowski, A., Lehtonen, J., Nordenswan, H. K., Mäyränpää, M. I., & Kupari, M. (2020). Idiopathic giant cell myocarditis or cardiac sarcoidosis? A retrospective audit of a nationwide case series. *ESC heart failure*, *7*(3), 1362–1370. https://doi.org/10.1002/ehf2.12725

11. Martens, C. R., & Accornero, F. (2021). Viruses in the Heart: Direct and Indirect Routes to Myocarditis and Heart Failure. *Viruses*, *13*(10), 1924. https://doi.org/10.3390/v13101924
12. Tschöpe, C., Ammirati, E., Bozkurt, B., Caforio, A. L. P., Cooper, L. T., Felix, S. B., Hare, J. M., Heidecker, B., Heymans, S., Hübner, N., Kelle, S., Klingel, K., Maatz, H., Parwani, A. S., Spillmann, F., Starling, R. C., Tsutsui, H., Seferovic, P., & Van Linthout, S. (2021). Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nature reviews. Cardiology*, *18*(3), 169–193. https://doi.org/10.1038/s41569-020-00435-x
13. Cadegiani F. A. (2022). Catecholamines Are the Key Trigger of COVID-19 mRNA Vaccine-Induced Myocarditis: A Compelling Hypothesis Supported by Epidemiological, Anatomopathological, Molecular, and Physiological Findings. *Cureus*, *14*(8), e27883. https://doi.org/10.7759/cureus.27883
14. Maisch, B., & Alter, P. (2018). Treatment options in myocarditis and inflammatory cardiomyopathy : Focus on i. v. immunoglobulins. Behandlungsoptionen bei Myokarditis und inflammatorischer Kardiomyopathie : Immunglobuline i. v. im Fokus. *Herz*, *43*(5), 423–430. https://doi.org/10.1007/s00059-018-4719-x