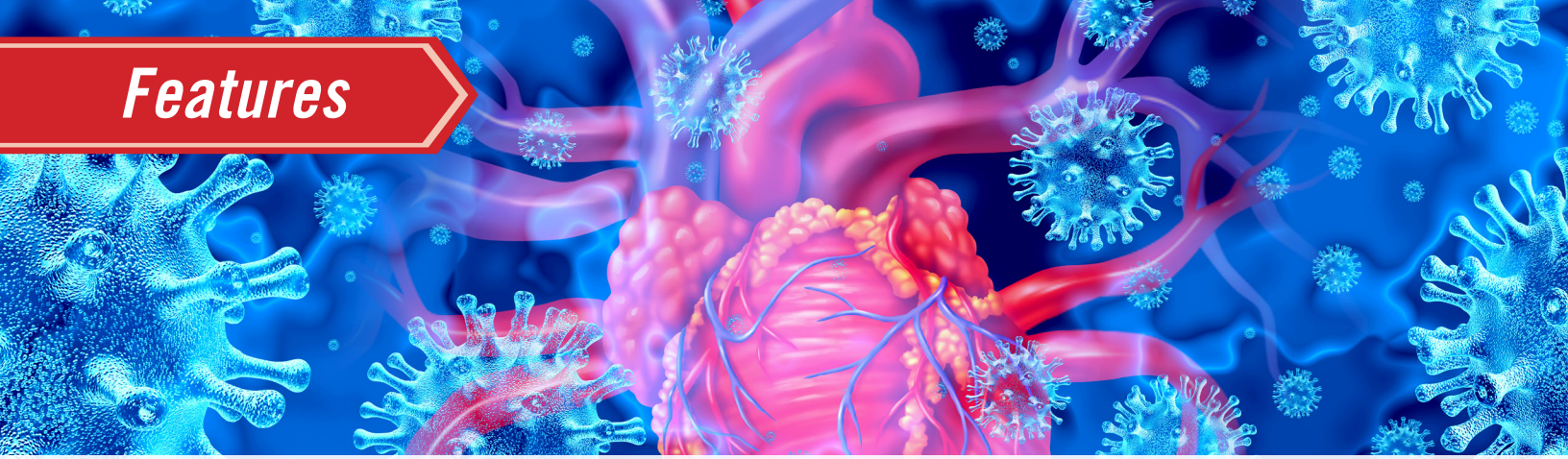


ID CORNER
Viral Myocarditis

by Ami Leigh Schmidt, 2023 PharmD Candidate, Etan Maistelman, 2023 PharmD Candidate, Kristen Bunnell, PharmD, BCCCP, BCIDP

Myocarditis, or inflammation of the myocardium of the heart, can be precipitated by a variety of infectious and noninfectious etiologies. Viruses are the most common cause of infectious myocarditis, a fact that has been highlighted in recent years by reports of patients who developed myocarditis following COVID-19 infection and vaccination. The objective of this manuscript is to review the epidemiology and treatment of viral myocarditis, with a focus on COVID-19.

Epidemiology

The global prevalence of myocarditis in 2017 was estimated to be 1.8 million cases, translating to approximately 15 cases per 100,000 people in North America.[1] The incidence in children is estimated to be 0.26-2.0 cases per 100,000 people, with the highest incidence in infancy and adolescence.[2]

Myocarditis is most commonly caused by viruses, but bacteria, fungi, and even parasites can play a role, especially in developing countries. In addition, noninfectious etiologies must be considered, which may be toxin-, medication-, or immune-mediated (Table 1).[3,4]

Clinical Presentation

Patients typically report cardiac symptoms of chest pain, dyspnea, or palpitations.[3-5] In cohort studies of patients with acute myocarditis, chest pain is a presenting symptom in 85%-90% of patients.[6,7] Patients may also endorse nonspecific symptoms, such as fatigue, fever, shortness of breath, myalgia, nausea, vomiting, or poor appetite. Most patients with myocarditis will recover fully from the disease, but approximately 20% of patients will develop inflammatory dilated cardiomyopathy.[8] Advanced cardiomyopathy from myocarditis may lead to left ventricular dysfunction and heart failure, ventricular arrythmias, or cardiogenic shock (fulminant myocarditis).[3] Myocarditis is thought to be an inciting factor in up to 10% of sudden cardiac deaths in children and young adults, and up to 20% of cases of sudden infant death syndrome.[5,9,10]

Diagnosis

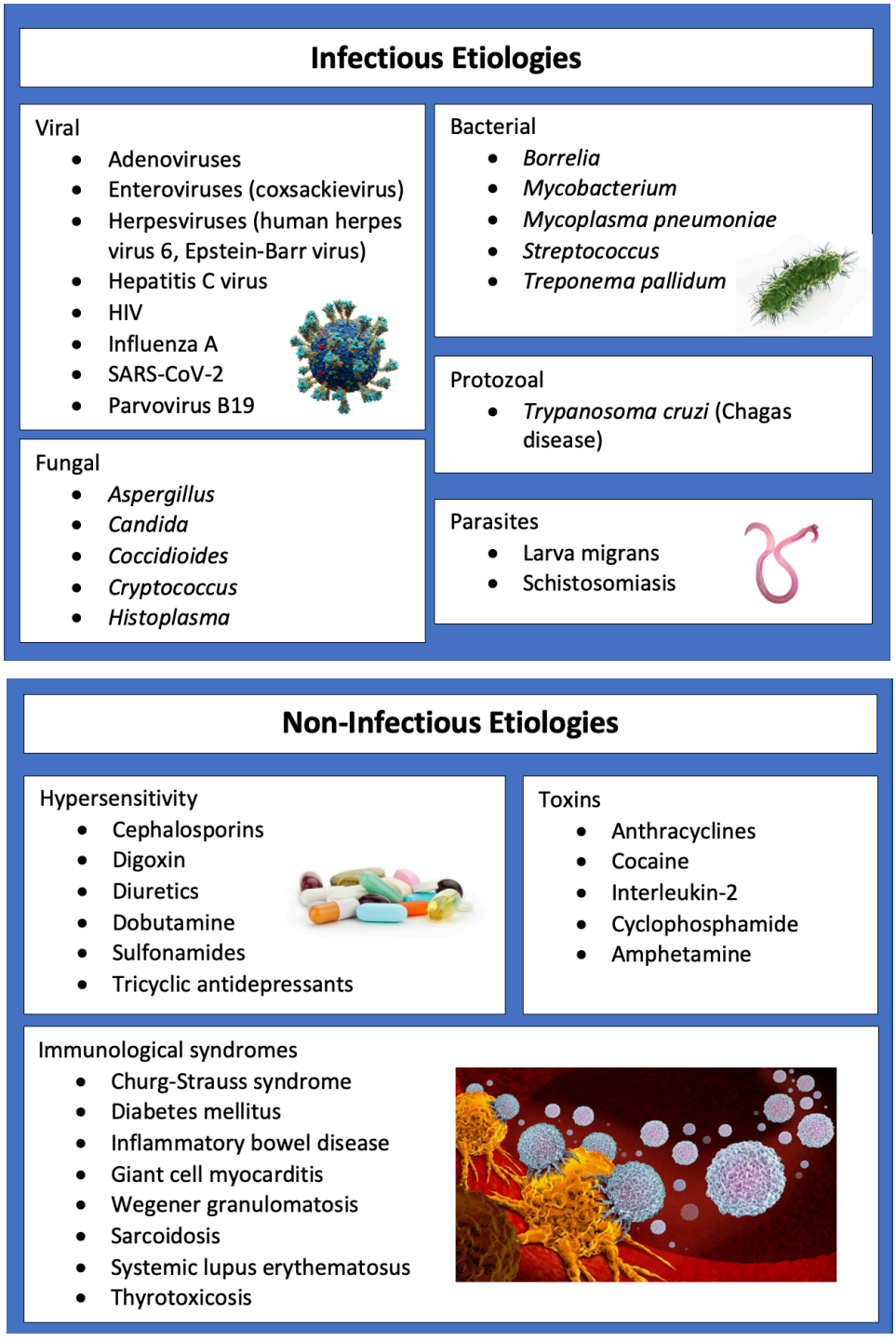
Viral myocarditis is typically a disease of exclusion from other inflammatory and cardiovascular conditions. Clinicians can use the Sagar criteria to classify myocarditis as possible, probable, or definite based on clinical symptoms, electrocardiogram (EKG) and echocardiogram findings, and cardiac enzymes.[4] In patients with myocarditis, labs show elevated inflammatory markers, troponin, and natriuretic peptides. A patient's EKG may have ST-segment elevation and wide QRS complex.[2,5] If the patient has progressed to cardiomyopathy, an echocardiogram will show left ventricle dysfunction or wall motion abnormalities. The gold standard diagnostic approach to myocarditis has historically been from histopathologic findings from an endomyocardial biopsy (EMB) of the right ventricular septal wall. Unfortunately, this procedure is invasive, and it is not always done in practice.[2] Experts suggest that EMB should be prioritized in patients with acute cardiomyopathy requiring inotropic agents or mechanical circulatory support, or acute arrythmias without clear cause.[5] Biopsy is the only way to determine the specific subtype of myocarditis, which has an implication for treatment approaches.[8] Patients who present with suspected myocarditis of a less severe magnitude may be candidates for cardiac magnetic resonance imaging (CMR), which has been shown to be highly sensitive and specific for the diagnosis of myocarditis in combination with lab and clinical data.[11] The American College of Cardiology Expert Consensus Decision Pathway defines myocarditis as: (1) the presence of cardiac symptoms such as chest pain and dyspnea, (2) an elevated cardiac troponin, and (3) abnormal EKG or echocardiogram, CMR with characteristic findings, and/or histopathologic confirmation on EMB.[12]

Pathophysiology

The most common viruses identified in myocarditis are coxsackie B3 virus, parvovirus B19, human herpes virus 6 (HHV6), human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr

virus, and influenza.[3,4] In the Marburg Myocarditis Registry, a large cohort of patients with suspected myocarditis who underwent EMB, parvovirus B19 was the most common cause of myocarditis and comprised 28% of cases.[13] In contrast, HHV6 and coxsackie virus comprised less than 1% of cases.[13] The virus that causes COVID-19, SARS-CoV-2, is also suspected to be a cause of viral myocarditis, as outlined below. Experts have distinguished between virus-mediated myocarditis and virus-triggered myocarditis to differentiate between viruses that are known to be directly cytotoxic to the myocardium, such as coxsackie virus, and those that exert their effects via immune mechanisms in the absence of viral material in the myocardium, such as influenza.[5] The initial phase of attempted viral clearance by the innate immune system lasts approximately 7 days.[3] After the acute phase, patients may clear the virus and achieve full recovery, experience sustained viremia, or develop persistent inflammation after viral clearance that progresses to dilated cardiomyopathy.[3] The inflammatory phase is autoimmune in nature, with recruitment of natural killer cells and macrophages and the release of pro-inflammatory cytokines like IL-1/IL-2, interferon-gamma, and tumor necrosis factor.[4] Cardiomyopathy is characterized by myocyte destruction and hypertrophy leading to decreased ejection fraction via increased left-ventricular end-diastolic pressure.

FIGURE 1. Infectious and Non-Infectious Etiologies of Viral Myocarditis



COVID-19 Infection

The exact incidence of myocarditis related to COVID-19 is unknown, but it appears to be uncommon.[14,15] A retrospective study of hospitalized patients with COVID-19 estimated the risk of new heart failure diagnosis to be less than 1%.[15] In prospective studies of athletes with asymptomatic or mild COVID-19 who were screened with CMR, the incidence of myocarditis ranged between 0.3% and –3.0%.[5] One of the largest retrospective reviews included data from 56,963 hospitalized patients with COVID-19 from 23 hospitals in the United States and Europe. The authors identified 97 patients with possible myocarditis, of whom 54 had definite or probable myocarditis diagnosed by EMB or CMR.[14] This translated to an estimated prevalence of 2.4 cases of myocarditis per 1,000 hospitalizations. In this cohort, patients with myocarditis typically presented with chest pain and dyspnea, and almost 40% had a fulminant presentation requiring inotropes or circulatory support. More than half of identified patients with myocarditis did not have concurrent COVID-19 pneumonia.[14]

COVID-19 Vaccinations

There have also been cases of myocarditis reported in patients who had received one of the COVID-19 mRNA vaccines manufactured by Pfizer or Moderna.[16-20] It is important to note that myocarditis is not a unique complication to the COVID-19 vaccine, having been reported in association with vaccines against smallpox, influenza, and hepatitis B with an incidence of 0.1%

from 1990 to 2018.[21] Of the myocarditis events that were reported to the Vaccine Adverse Event Reporting System (VAERS) between December 2020 and August 2021, the majority of cases occurred after the second vaccine in young (median age 21) males with a median time to symptom onset of 2 days.[22] As of May 2022, verified VAERS reports indicated that the highest risk of myocarditis occurred in individuals 16-17 years of age, in which there were 298 verified reports after 12,687,076 doses (0.002%).[16] The American College of Cardiology notes that the clinical benefits of COVID-19 vaccination outweigh the risks of myocarditis, even among those at highest risk for myocarditis.[12] A recent conference abstract described the risk of post-vaccination myocarditis in children as being similar to the risk of being struck by lightning.[23] The majority of patients with reported myocarditis had a resolution of symptoms after initial hospitalization, with 87% of patients reported to VAERS experiencing a resolution of their presenting symptoms by hospital discharge.[22]

Treatment

There are no specific clinical practice guidelines for myocarditis treatment. Guidelines for the management of heart failure and arrhythmias should guide management where applicable, with treatments including beta blockers, renin-angiotensin system inhibitors, aldosterone antagonists, or diuretics. Expert consensus documents have been published by the American College of Cardiology specific to COVID-19-related myocarditis and by an international expert panel related to general myocarditis management.[5,12]

Patients with chronic autoimmune inflammatory cardiomyopathy who are known to be virus negative on EMB may benefit from immunosuppression with prednisone and azathioprine, but it is less clear whether the benefit extends to those with viral myocarditis.[8] Consensus statements recommend intravenous corticosteroids in the case of advanced or fulminant myocarditis with decompensated heart failure, or if high suspicion for autoimmune myocarditis exists.[5,12] Antiviral agents also do not have a clearly defined role in viral myocarditis. The betaferon in chronic viral cardiomyopathy (BICC) trial is one of the few studies to investigate a role of antiviral therapy—specifically, whether interferon beta-1b would benefit patients with heart failure from viral myocarditis. Patients, all of whom had confirmed adenovirus, enterovirus, or parvovirus B19, experienced enhanced viral clearance and improved quality of life and patient global assessment.[24] That said, antivirals are not specifically endorsed by either expert consensus document at this time due to the small body of evidence.[5,12]

The ACC Consensus Decision Pathways notes that fulminant myocarditis should be managed the same as cardiogenic shock from other etiologies, and that intravenous corticosteroids can be considered. Corticosteroids are also suggested in those with biopsy proven severe myocardial inflammatory infiltrates, with the caveat that these findings have rarely been reported with COVID-19. Patients with associated myopericarditis may be treated with low-dose colchicine or prednisone.[4,12] The recommendation to use nonsteroidal anti-inflammatory drugs (NSAIDs) remains a controversial issue. NSAIDS may be helpful to treat pain associated with pericarditis, but patients with left ventricular dysfunction are typically advised to avoid NSAIDS. In addition, athletes who are diagnosed with COVID-19-related myocarditis are advised to refrain from exercise for 3-6 months.[12]

Conclusion

Myocarditis is a rare complication of viral infections, including COVID-19, as well as mRNA-based COVID-19 vaccinations. Clinicians should have a high index of suspicion for myocarditis among patients with recent viral illness or COVID-19 vaccination who endorse symptoms of chest pain, dyspnea, and palpitations and who have nonspecific complaints including fever and fatigue. Diagnosing myocarditis in such patients requires laboratory evidence of myocardial damage and compatible findings on EKG, echocardiogram, CMR, and/or EMB. Treatment of myocarditis is largely supportive for dilated cardiomyopathy, but corticosteroids and other immunomodulatory agents could be considered in select populations. Clinicians should be advised that best practices in the management of viral myocarditis are still evolving.

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