

COMPENDIUM ON COVID-19 AND CARDIOVASCULAR DISEASE

Vaccination-Associated Myocarditis and Myocardial Injury

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ABSTRACT: SARS-CoV-2 vaccine–associated myocarditis/myocardial injury should be evaluated in the contexts of COVID-19 infection, other types of viral myocarditis, and other vaccine-associated cardiac disorders. COVID-19 vaccine–associated myocardial injury can be caused by an inflammatory immune cell infiltrate, but other etiologies such as microvascular thrombosis are also possible. The clinical diagnosis is typically based on symptoms and cardiac magnetic resonance imaging. Endomyocardial biopsy is confirmatory for myocarditis, but may not show an inflammatory infiltrate because of rapid resolution or a non-inflammatory etiology. Myocarditis associated with SARS-CoV-2 vaccines occurs primarily with mRNA platform vaccines, which are also the most effective. In persons aged >16 or >12 years the myocarditis estimated crude incidences after the first 2 doses of BNT162b2 and mRNA-1273 are approximately 1.9 and 3.5 per 100 000 individuals, respectively. These rates equate to excess incidences above control populations of approximately 1.2 (BNT162b2) and 1.9 (mRNA-1273) per 100 000 persons, which are lower than the myocarditis rate for smallpox but higher than that for influenza vaccines. In the studies that have included mRNA vaccine and SARS-CoV-2 myocarditis measured by the same methodology, the incidence rate was increased by 3.5-fold over control in COVID-19 compared with 1.5-fold for BNT162b2 and 6.2-fold for mRNA-1273. However, mortality and major morbidity are less and recovery is faster with mRNA vaccine–associated myocarditis compared to COVID-19 infection. The reasons for this include vaccine-associated myocarditis having a higher incidence in young adults and adolescents, typically no involvement of other organs in vaccine-associated myocarditis, and based on comparisons to non-COVID viral myocarditis an inherently more benign clinical course.

Key Words: disorder ■ infection ■ inflammatory disease ■ mRNA vaccine-associated myocarditis

Myocarditis, originally defined by the WHO as an inflammatory disease of the myocardium diagnosed by established histological, immunological, and immunohistochemical criteria,^{1,2} is a relatively common and potentially serious disorder that has assumed an important position as a complication of both COVID-19 infection and vaccination against the offending pathogen, SARS-CoV-2. There are common as well as unique features of the various types of myocarditis, including those associated with SARS-CoV-2 infection and mRNA COVID-19 vaccine. Table 1 lists many of the types of myocarditis, the most common of which in developed countries is virus-induced.^{2,9}

Early reports of incident myocardial injury during the COVID-19 pandemic hastened an update in the

diagnostic approach to myocarditis, taking advantage of progress in imaging and biomarker analytic capabilities. While myocarditis diagnostic criteria initially consisted of histologic, immunologic and immunohistochemical data such as that described in 1987 in the original Dallas Criteria,^{10,11} a plethora of imaging and biomarker modalities now exists. Cardiac MRI (CMR) and positron emission tomography-computerized tomography imaging have become prominent in the diagnostic evaluation, and biomarkers such as high sensitivity troponin assays can rapidly and definitively provide evidence of myocardial injury. Despite these advancements, the true etiology and histopathologic characterization of myocarditis and myocardial injury may remain unclear. In these cases, endomyocardial biopsy (EmBx) remains the gold standard for diagnosis.

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Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance imaging
LGE	late gadolinium enhancement
MIS-C	multisystem inflammatory syndrome in children

CLINICAL FEATURES OF INFLAMMATORY MYOCARDIAL DISEASES

The diagnosis of myocarditis is based on the presence of (1) cardiac symptoms, including chest pain, dyspnea, palpitations, or syncope; (2) biomarker evidence of myocardial injury, typically provided by an elevated troponin level; (3) abnormal ECG, CMR, positron emission tomography-computerized tomography or echocardiographic findings; (4) histopathologic findings of an inflammatory process on biopsy or autopsy; (5) the absence of flow limiting coronary artery disease.⁶ Of these components, CMR has assumed an important role in diagnosis but also in prognosis.^{12,13} Despite the evidence that in most cases myocarditis is a mild disease with good prospects for full recovery,¹⁴ 1 study has reported a 10-year mortality rate of 39% in patients with biopsy-proven myocarditis.¹⁵

Evidence of myocardial injury does not necessitate a diagnosis of myocarditis. When a cardiac troponin level is over the 99th percentile of the upper reference limit,⁶ there exists a spectrum of myocardial injury, including in the context of COVID-19 and vaccine-related cardiac sequelae, that is not myocarditis. These disorders include stress cardiomyopathy (Takotsubo), microinfarction, or ischemic injury due to microvascular thrombosis and hypoxemia-related cardiac stress.

The incidence of myocarditis has risen in the past decade, with a US-based national inpatient database analysis estimating an increase from 9.5 reported cases per 100 000 in 2005 to 14.4 per 100 000 in 2014.¹⁶ The incidence of cardiogenic shock in this cohort also rose, from 6.9% in 2005 to 12% in 2014, without an attendant increase in mortality likely due to the increased utilization of ECMO and percutaneous mechanical support devices during this period.¹⁶ The incidence of non-Covid viral myocarditis is higher in infants, adolescents, and young adults, and more prevalent in males than females.¹⁷

The clinical course of myocarditis is highly variable, ranging from mild chest discomfort to fulminant disease with cardiogenic shock and life-threatening hemodynamic dysfunction. In a multicenter retrospective registry, rates of cardiac mortality or heart transplantation in patients presenting with acute myocarditis were 3.0% and 4.1% at 1 and 5 years, respectively.¹⁴ However, in patients who presented with LVEF <50%, sustained ventricular arrhythmias, and cardiogenic shock requiring

inotrope or mechanical circulatory support (fulminant myocarditis), rates of cardiac mortality or heart transplantation were 11.3% and 14.7% at 1 and 5 years, respectively.¹⁴ The observation that giant cell myocarditis is a particularly nefarious entity with a worse prognosis than presentations such as eosinophilic and lymphocytic myocarditis¹⁸ emphasizes the importance of EmBx in determining the etiology and prognosis of specific types of myocarditis.

CARDIAC IMAGING IN MYOCARDITIS

The processes of acute injury and inflammation defined as myocardial tissue edema that transitions into myocyte loss and fibrotic replacement with increased extracellular space are key pathologic features for which CMR can define, using tissue-specific T1 and T2 magnetic properties. A consensus group proposed criteria in Lake Louise 2009 using CMR as a non-invasive biopsy based on its inherent capability of characterizing differences in cell and tissue water/collagen content.¹² With a CMR approach, the diagnosis of *suspected myocarditis* is made by merging clinical symptoms and presentation with fulfillment of CMR criteria that assess myocardial water (edema) content (T2 weighted images and T1/T2 mapping of relaxation times), the degree of extracellular and intravascular volume (early gadolinium enhancement of T1 weighted images), and evidence of necrosis or fibrosis via late gadolinium enhancement (LGE).¹⁹ Although larger studies are needed, abnormalities in 2 of 3 of these measurements or in 2 of 2 if EGE is not measured has a predictive accuracy of in the 80% range using EmBx for confirmation.^{6,19} In addition to tissue characterization, CMR produces excellent measurements of ventricular volumes, ejection fraction, and longitudinal strain, providing concurrent information on LV and RV function.

Based on CMR imaging, there appears to be variability of the injury/inflammation in myocarditis resulting in heterogeneous patterns of LGE. Generally, myocarditis appears to preferentially affect ventricular mid- and sub-epicardium not in a coronary vascular distribution. In addition, distinct patterns of LGE may be present as shown in Figure 1. For example, the LGE pattern of eosinophilic myocarditis (Figure 1A) tends to be biventricular affecting the subendocardial myocardium and often is associated with complex ventricular thrombi. In comparison inflammatory myocarditis from giant cell infiltration tends to localize to the mid myocardial septum (Figure 1B), and in this case was associated with mild to moderate LV dysfunction (LVEF=38%). A punctate focal LGE pattern appears mid myocardial and subepicardial in vaccine-associated inflammation in Figure 1C, and a less extensive but similar pattern of LGE is shown for a COVID-19 associated myocarditis patient in Figure 1D.

Table 1. Types of Myocarditis

Myocarditis type	Examples	Clinical course and clues	Diagnostic findings	Potential therapeutic interventions
Lymphocytic	Viral, bacterial, fungal	Variable—chest pain through fulminant heart failure and cardiogenic shock	ECG: ST-segment elevations	Supportive care; no clear evidence for benefit of corticosteroids. If fulminant presentation, inotropic support +/- mechanical circulatory support, heart transplantation
			Imaging: normal or reduced EF, LGE on CMR	
			Biomarkers: elevated troponin, CRP	
			Histology: lymphocyte-predominant infiltrate	
Giant cell	Unknown	Rapidly progressive heart failure, cardiogenic shock, arrhythmias, atrioventricular block	ECG: conduction abnormalities, ventricular arrhythmias.	Immunosuppression, inotropes, mechanical circulatory support, heart transplantation
			Biomarkers: elevated troponin. Imaging: reduced biventricular function	
			Histology: multinucleated giant cells with lymphocytic infiltrate	
Eosinophilic	Hypereosinophilic syndrome due to medications, EGPA, hypereosinophilic syndrome, myeloproliferative eosinophilia, infections ^{3,4}	Dyspnea, chest pain, fever	ECG: ST-segment elevation.	Corticosteroids and immunosuppression, inotropic support, stop possible causative drug, anticoagulation ^{3,4}
			Biomarkers: Elevated CRP, troponin, peripheral eosinophilia	
			Imaging: reduced LVEF, pericardial effusion, ventricular thrombi, LGE on CMR	
Toxin-induced-ICIs	ICIs	Myositis, conduction abnormalities (heart block)	ECG: AV and interventricular conduction delay. Biomarkers: elevated troponin	Stop ICI, high-dose corticosteroids, abatacept in clinical trials ⁵
			CMR: LGE in myocarditis pattern	
			Histology: T-cell predominant lymphocytic infiltrate	
COVID-19	COVID-19 infection	Chest pain, heart failure, dyspnea. May occur with or without COVID pneumonia	ECG: ST-segment elevation.	Supportive care, steroids if concurrent pneumonia or MIS-A, mechanical support for cardiogenic shock ⁶
			Biomarkers: Elevated troponin, CRP, D-dimer	
			Imaging: Normal or reduced EF, variable/patchy LGE on CMR	
			Histology: lymphocytic infiltrates	
SARS-CoV-2 vaccine associated	Usually within 21 days of mRNA vaccine (BNT162b2 or mRNA-1273) ^{7,8}	Chest pain, fever, dyspnea	ECG: ST-segment elevation	Supportive care, steroids/colchicine for hemodynamic instability and pericarditis, mechanical support for cardiogenic shock ⁶
			Biomarkers: elevated troponin.	
			Imaging: normal or reduced EF. Punctate focal LGE on CMR	

AV indicates atrioventricular; CRP, C-reactive protein; CMR, cardiac magnetic resonance imaging; EF, ejection fraction; EGPA, eosinophilic granulomatosis with polyangiitis; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.

HISTOPATHOLOGY

Histopathology of myocarditis varies depending on its etiology, with the common feature being the presence of inflammation with associated myocyte injury or necrosis that is nonischemic in nature. Borderline myocarditis is diagnosed when there is a sparse inflammatory infiltrate without evidence of myocyte damage.^{10,11} While myocarditis is often suspected based on clinical presentation and imaging, EmBx is still considered the gold standard for diagnosis.²⁰ However, the sensitivity of EmBx in cases of suspected myocarditis is low and false negative rates are high, secondary to the relatively small size of biopsies, sampling error due to patchy distribution of the disease, and interobserver variability as to whether diagnostic criteria are met.^{21,22} Despite these drawbacks, EmBx is often performed, as it allows not only for confirmation of myocarditis, but further classification as to the specific histotype.

Lymphocytic myocarditis is characterized by a T-lymphocyte predominant infiltrate with scattered B-lymphocytes and macrophages (Figure 2A), and arises most frequently as a consequence of viral infection or postviral autoimmune response.²³ Histologic findings are generally nonspecific, though immunohistochemistry directed toward specific viruses is often employed to obtain an etiologic diagnosis. Giant cell myocarditis (GCM) demonstrates characteristic giant cells (Figure 2B) as well as a prominent eosinophilic infiltrate in addition to lymphocytes and macrophages. The acute/active phase of GCM demonstrates intense inflammation and scattered giant cells, often with striking myocyte necrosis.²⁴ Eosinophilic myocarditis is characterized by infiltration of the endocardium and myocardium by mixed inflammation with eosinophils (Figure 2C) and has a variety of etiologies including drug/hypersensitivity reactions, parasitic infections, and hypereosinophilic syndrome²⁵ and often follows a fulminant course.²⁶

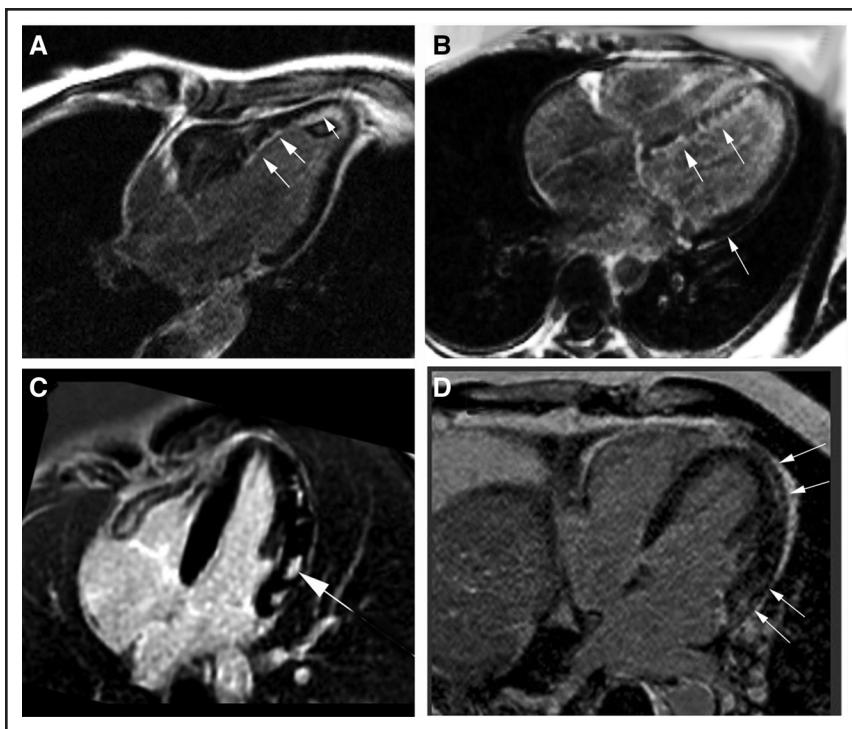


Figure 1. Myocarditis appears in different imaging forms as shown in this 4-chamber view of late gadolinium enhanced (LGE) cardiac magnetic resonance imaging (CMR) images.

Eosinophilic myocarditis (**A**) when imaged using LGE has unique subendocardial enhancement of the ventricles (arrows) as a hematologic/immune process. Also common in this type of myocarditis is thrombus formation (smaller arrow, dark within apical chamber). Immune/inflammatory myocarditis (**B**) tends to be more diffuse affecting the lateral wall, entire septum (arrows), and RV in this case of giant cell myocarditis. Note the focal almost punctate LGE of the lateral and apical walls in a case of vaccine associated myocarditis (**C**) compared with more diffuse basal and apical linear LGE of lesser intensity of the lateral myocardium in a case of COVID-19 myocarditis (**D**); this patients' CMR was performed 8 days after a positive SARS-CoV2-PCR, at a time when the patient was having chest pain.

Myocarditis Associated With COVID-19 Infection

Most cases of COVID-19 myocarditis are diagnosed via clinical presentation and imaging, but a number of cases have also been confirmed histopathologically, via either EmBx or on autopsy. Findings have included nonspecific abnormalities, inflammation with limited myocyte necrosis, and inflammatory infiltrate with

associated myocyte necrosis that meet full diagnostic criteria for myocarditis.^{3,27,28} While findings diagnostic of myocarditis have been relatively infrequent in many series, several cases have demonstrated PCR-detectable viral antigens, even in the absence of myocarditis.⁴ The inflammation within positive cases is similar to myocarditis associated with other viruses, with a mixed infiltrate of lymphocytes and macrophages (Figures 2D and 3A).²⁹ In a number of cases, increased interstitial

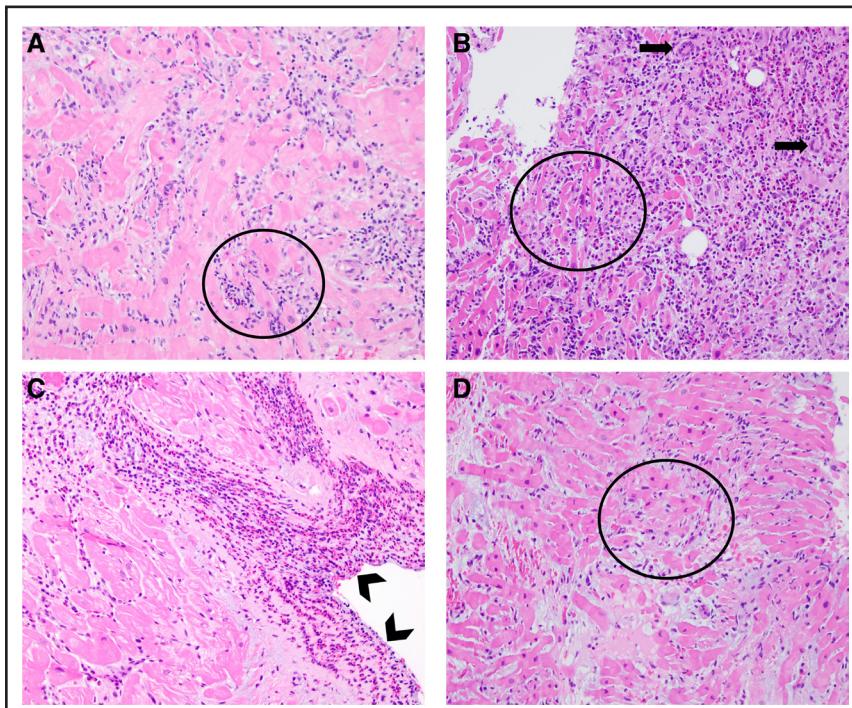


Figure 2. Endomyocardial biopsies of myocarditis histotypes (H&E, 200×).

A. Lymphocytic myocarditis. **B.** Giant cell myocarditis, arrows highlight giant cells. **C.** Eosinophilic myocarditis, arrowheads highlight endocardial involvement by eosinophils. **D.** COVID-19 myocarditis, from study by Altman et al.²⁹ Circles highlight areas of myocyte damage.

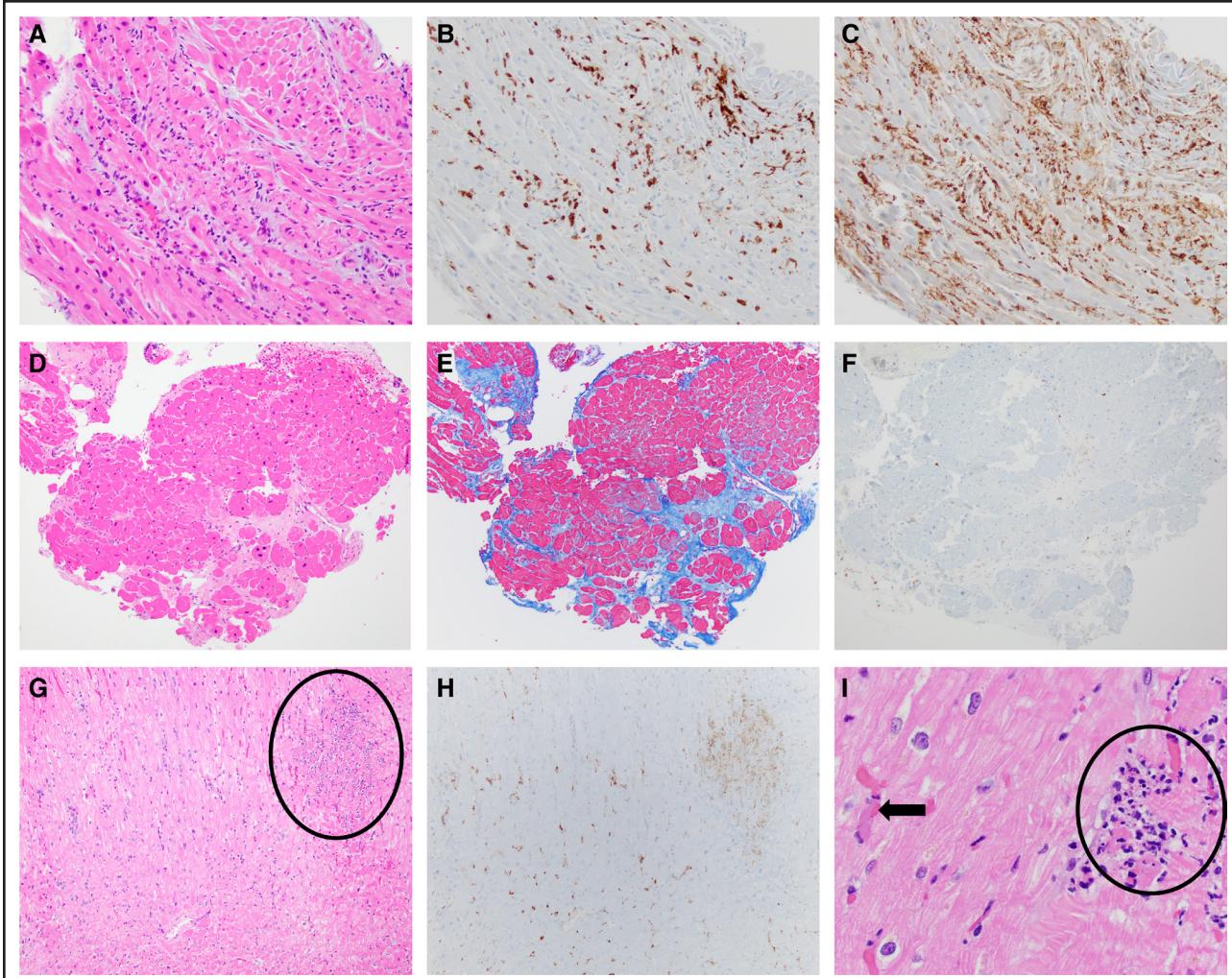


Figure 3. Endomyocardial biopsies from clinically diagnosed COVID-19 myocarditis cases.

A, COVID-19 myocarditis, histologically confirmed (H&E, 200 \times). **B**, CD3 immunostain highlighting T-cells (200 \times). **C**, CD68 immunostain highlighting macrophages (200 \times). **D**, Possible resolved COVID-19 myocarditis with interstitial fibrosis (H&E, 100 \times), cardiac magnetic resonance imaging from 40 days earlier exhibited findings of myocarditis (Figure 1D). **E**, Trichrome stain highlighting fibrosis from likely resolved COVID-19 myocarditis (100 \times). **F**, CD45 immunostain demonstrating lack of lymphocytes in resolved COVID-19 myocarditis (100 \times). **G**, Microinfarct (circle) in patient clinically diagnosed with COVID-19 myocarditis (100 \times). **H**, CD68 immunostain highlighting scattered interstitial macrophages, including in the area of microinfarct (100 \times). **I**, Microinfarct (circled) with associated necroinflammatory debris and adjacent capillary (arrow) showing fibrin thrombus (600 \times). Microinfarct (circled) with associated necroinflammatory debris and adjacent capillary (arrow) showing fibrin thrombus (600 \times).

macrophages without associated myocyte injury have been the most prominent finding. Immunohistochemically, a majority of the cells are CD3-positive T-lymphocytes (Figure 3B) and CD68-positive macrophages (Figure 3C), with a smaller component of CD20-positive B-lymphocytes; giant cells, and granulomas are absent. Eosinophils have been rarely reported in COVID myocarditis, with 1 report of fatal eosinophilic myocarditis in an adolescent.³⁰ Further characterization of the T-lymphocytes has demonstrated some cases to be CD4 (helper) T-lymphocyte predominant, while other cases are CD8 (cytotoxic) T-lymphocyte predominant.³¹ Hearts biopsied after treatment or resolution of inflammation may demonstrate nonspecific changes suggesting resolution of an active process including

fibrosis without evidence of an inflammatory infiltrate (Figure 3D through 3F). In situ hybridization has demonstrated SARS-CoV-2 RNA in interstitial cells and macrophages,³² and ultrastructural examination has revealed rare cases where viral particles are present in cardiac endothelial cells.^{33,34}

Histopathologic etiologies other than direct myocardial damage should be considered as a feature of any case of myocarditis that has been diagnosed clinically or via imaging. COVID-19 demonstrates a propensity for thromboembolic events with subsequent ischemic damage. Fibrin and platelet thrombi have been identified in small intramyocardial blood vessels, though they are less frequently seen in larger coronary arteries.³⁵ The possibility for small vessel thrombosis initiating downstream

ischemic changes has been reported,³⁶ as well as seen in our experience (Figure 3G through 3I). These alternate etiologies for myocardial damage should be considered in the context of the clinical picture as possibilities to explain troponin elevation in cases where EmBx is negative for myocarditis.

NONCOVID VACCINE-ASSOCIATED MYOCARDITIS

Adverse effects have been associated with most, if not all, vaccinations that are used to protect against infectious diseases. Common adverse effects (frequency 1%–10%) associated with vaccination include short-lived discomfort at injection sites (reactogenic symptoms) and postvaccination flu-like symptoms (fever, chills, and myalgias). The risk of serious adverse effects after vaccination is very low with incidences typically less than 10 per 100 000 vaccine doses in most cases. Serious adverse effects associated with vaccinations include cardiac effects such as myocarditis and pericarditis and noncardiac effects such as anaphylaxis, febrile seizures, immune thrombocytopenia, encephalitis, meningitis, and Guillain-Barre syndrome. A recent analysis by the WHO identified 790 vaccine-related cases of myocarditis out of 5108 drug-induced myocarditis cases (15.5%) across 47 countries from 1967 to 2020.³⁷ In 2010, there was an increase of myocarditis cases ($n=294$) after vaccination including 177 (60.2%) associated with smallpox, 72 (24.5%) with anthrax, and 48 (16.3%) with influenza.³⁷ Another study estimated that the incidence of myocarditis following smallpox vaccination (13.2 per 100 000 vaccine doses) is much higher than the incidence following COVID-19 vaccination (Table S1; per 100 000 persons receiving the first 2 doses, median of 1.9 for BNT162b2, 3.5 for mRNA-1273), influenza vaccination (0.13 per 100 000 vaccine doses), or other non-small pox vaccinations (5.7 per 100 000 vaccine doses).³⁸ Myocarditis following vaccination typically has a short time to onset (average of 10 days), low mortality, and often has pericardial involvement.³⁷

Myocarditis following Smallpox Vaccine

Smallpox vaccination with vaccinia (a live orthopox virus) was used throughout the 19th and 20th centuries in a worldwide campaign that eliminated the disease by 1979.³⁹ During the later stages of this campaign, post-vaccination myocarditis was described, with an incidence of 2% to 3% noted in Swedish military recruits^{40,41} and 1 in 10 000 in a 1983 study in Finland.^{42,43} In 2002, in response to concerns that smallpox could be used as a bioterrorism weapon, the United States government initiated smallpox vaccination programs for military personnel and civilians with occupations related to responses to bioterrorism. Both programs administered Dryvax, a live-virus formulation of vaccinia virus prepared from calf

lymph.⁴⁴ In the United States military vaccination program, 18 cases of probable myocarditis were identified between December 2002 and March 14, 2003 among 230 734 primary smallpox vaccine recipients (incidence of 7.8 per 100 000 over 30 days).⁴⁵ Myocarditis cases occurred primarily in young (mean age 26.5 years), white males with symptom onset occurring 7 to 19 days after vaccination.⁴⁵ In the civilian program from January through October 2003, there were 21 cases of myopericarditis within 3 months after vaccination (incidence 55 per 100 000). Median age was 48 years and onset of symptoms occurred 11 days (range 2–42 days) after vaccination.⁴⁶ The majority of myocarditis cases among civilians (86%) were re-vaccinees.⁴⁶

The clinical presentations of myocarditis following smallpox vaccination ranged from asymptomatic to heart failure and shock. Military personnel experienced more severe disease manifestations than their civilian counterparts, with elevated biomarkers, abnormal electrocardiograms and echocardiograms showing myocardial dysfunction; non-military personnel had milder symptoms and evidence of less myocardial injury^{45–47} that were attributed to differences in age, sex, stress, and exercise levels. Due to the increased incidence of myocarditis including 2 fatal outcomes, the CDC now recommends against smallpox vaccination for persons with heart disease, history of ischemic cardiovascular disease, or multiple cardiac risk factors.⁴⁸

Myocardial biopsy in 1 case of myocarditis after smallpox vaccination in the military program revealed histological evidence of eosinophil infiltration of the myocardium, eosinophil degranulation, secretion of major basic protein in close apposition to myocyte necrosis, and IL-5 generation.⁴⁵ Murphy et al⁴⁶ also reported a case of eosinophilic lymphocytic myocarditis on EmBx after smallpox vaccination. In another case, a mixed mononuclear infiltrate was observed.⁵⁰ However, a CDC report of myopericarditis cases after the smallpox vaccine among military personnel and civilians in 2003 found no evidence of myopericarditis among the 3 cardiac tissue samples evaluated.⁴⁸ The mechanism for myocarditis associated with smallpox vaccine is unclear. Vaccine-mimicry of myocardium antigens and aberrant activation of toll-like receptors have been proposed.⁵¹

Currently, the JYNNEOS vaccine, a replication-deficient vaccinia virus vaccine, is approved to prevent both smallpox and monkeypox. JYNNEOS has been used widely in the United States during the 2022 monkeypox outbreak and appears to be a safer alternative to older vaccinia-based vaccines. To date, JYNNEOS vaccine has not been linked to the development of myocarditis.

Myocarditis Following Influenza Vaccine

Influenza vaccine has rarely been associated with post vaccination myocarditis.^{52,53} A recent prospective study of influenza and smallpox vaccine recipients found that the

incidence of myocarditis/pericarditis after smallpox vaccination was more than 200-times higher than the background rate, but among influenza vaccine recipients, there were no confirmed myocarditis cases.⁵³ A recent meta-analysis of the influenza myocarditis incidence yielded a rate of 0.13 (0.0–88.4) per 100 000,³⁸ a value likely at or below the background myocarditis rate. Thus, myocarditis following influenza vaccine is not a current concern.

SARS-COV-2 VACCINE-ASSOCIATED MYOCARDITIS AND MYOCARDIAL INJURY

COVID-19 Vaccine Platforms and Formulations

The global response to the COVID-19 pandemic necessitated the rapid development and implementation of vaccines to protect against SARS-CoV-2 infection and its clinical consequences. As of November 10, 2022, the WHO had granted emergency use listing for eleven COVID-19 vaccines. These vaccines differ by antigenic target (SARS-CoV-2 Spike S1 subunit versus inactivated whole virus). The Spike S1 vaccines also differ by the antigen delivery platform (mRNA coding for S1, adenovirus vector expression of S1, or purified S1 protein subunit). The WHO listed vaccines are summarized in Table 2.⁵⁴ It is estimated that COVID-19 vaccines saved over 20 million lives within the first year of implementation,⁵⁵ and mRNA vaccines were considered highly efficacious on the basis of reducing infection in their Phase 3 clinical trials that were conducted before the emergence of resistant CoV-2 variants.

In the United States, 4 vaccines (BNT162b2/Comirnaty, Ad26.COV2.S/Jcovin, NVX-CoV2373/Nuvaxoid, mRNA-1273/Spikevax) have received emergency use authorization, and over 685 million vaccine doses have been administered. Over 97% of all COVID-19 vaccine doses administered in the United States have been an mRNA platform vaccine (BNT162b2/Comirnaty or mRNA-1273/Spikevax). These mRNA platform vaccines contain an *in vitro* transcription produced mRNA that is structurally similar to cellular mRNA molecules. Both vaccine mRNAs have an open reading frame for the SARS-CoV-2 Spike S1 subunit flanked by 5' and 3' untranslated regions, a methylguanosine cap on the 5' end, and a polyadenylated tail on the 3' end. During *in vitro* transcription novel nucleosides with base modifications are incorporated in the mRNA to provide resistance to degradation by cellular RNases and reduce aberrant immune responses.⁵⁶ In addition, the S1 open reading frame has been modified to include 2 proline residues that stabilize the receptor binding domain in an open prefusion confirmation.⁵⁷ In addition to mRNA, both BNT162b2 and mRNA-1273 contain lipid nanoparticles to improve mRNA stability and delivery to cells after intramuscular injection.⁵⁸ Remarkably, due to the relative simplicity of the manufacturing process, initial animal experiments were completed within 2 months after the spike coding sequence was identified.⁵⁹

After intramuscular administration, a COVID-19 mRNA vaccine, the lipid nanoparticle encapsulated mRNAs cross lipid-enriched cell membranes and enter the cytoplasm likely facilitated by binding to cell surface lipoprotein (LDL) receptors.⁶⁰ In the cytoplasm, ribosomes translate full-length S1 Spike glycoproteins,⁶¹ which are subsequently broken down by proteasomes and concentrated at cell membranes or transported outside of the cell to stimulate immune cell and antibody production. Antigen-presenting cells engulf S1 and present the antigen to T-cells. B cells and CD4 cells are also activated, producing neutralizing antibodies and long-term vaccine-mediated immunity.⁶²

General Pathobiology

For both COVID-19 infection and vaccine-associated myocarditis, there are several ways in which exposure to SARS-CoV-2 antigen can theoretically injure the heart, all of which tend to be aggregated into a clinical diagnosis of myocarditis or myopericarditis.²⁹ These include an inflammatory myocardial process that may or may not include the pericardium, coronary macrovascular or microvascular thrombosis, apparent direct myocardial injury, and proarrhythmic electrophysiologic effects. All of these may be detectable at the biomarker level by elevated circulating levels of cardiac myocyte sarcomeric or cytoplasmic proteins, such as troponins or natriuretic peptides. Among these various mechanisms, a myocardial inflammatory process has been the most frequently diagnosed condition, although rarely biopsy proven.

Of the vaccines and platforms that have been deployed against COVID-19 (Table 2), the mRNA vaccines BNT162b2 and mRNA-1273 have definitively been associated with an increased rate of myocarditis and pericarditis or both (myopericarditis), and with the possible exception of NVX-CoV2373 recombinant spike protein (Nuvaxoid) the other vaccines have not. Although myocarditis has been reported following vaccination with NVX-CoV2373, its very recent authorization for use precludes any meaningful assessment of myocarditis risk.

For the mRNA platform vaccines, as of November 21, 2022, the respective doses of BNT162b2 or mRNA 1273 administered have been: U.S., 387M, and 255 M; Japan, 255 M and 80 M; EU, 653 M and 153M.⁶³ Clearly, these are blockbuster, life-saving biologics that are being administered at an unprecedented rate, and any potential serious adverse event associated with them needs to be subjected to careful scrutiny.

Incidence

At present, the risk of myocarditis from COVID-19 vaccines that exceeds the risk of control population background inflammatory myocardial disease is limited to mRNA platform products, with the recombinant Spike

Table 2. COVID-19 Vaccines

Vaccine	Manufacturer	Antigen	Platform	Efficacy estimate*	Reported myopericarditis
WHO approved					
BNT162b2 (Comirnaty)	Pfizer/BioNTech	Spike	mRNA/lipid nanoparticle	95%	Yes
				86% in 65+	
Convidencia	CanSino	Spike	Adenovirus vector	66%	Not reported
Coronavac	Sinovac	Whole virus	Inactivated virus	50%	Not reported
Covavax	Serum Institute of India	Spike	S1 protein subunit	90%	Not reported
Covaxin	Baharat Biotech	Whole virus	Inactivated virus	78%	Yes
Covilo	Sinopharm	Whole virus	Inactivated virus	78.9%	Not reported
Covishield	Serum Institute of India	Spike	Adenovirus vector	81%	Not reported
Ad26.COV2.S (Jcovin)	Janssen/ Johnson&Johnson	Spike	Adenovirus vector	72%	No
				86% against severe disease	
NVX-CoV2373 (Nuvaxovid)	Novavax	Spike	S1 protein subunit/ saponin adjuvant	90.4%	Yes
				78.6% in 65 plus	
mRNA-1273 (Spikevax)	Moderna	Spike	mRNA/lipid nanoparticle	94%	Yes
				86% in 65+	
ChAdOx1 (Vaxzevria)	Oxford/AstraZeneca	Spike	Adenovirus vector	70%	Yes
Not WHO approved but widely used					
Sputnik/Gam-COVID-Vac	Gamaleya Research Institute	Spike	Adenovirus vector	91.6%	Yes

*Effectiveness against disease at the time of clinical trial. Variants had not emerged before the publication of many vaccine efficacy data results. Direct comparison of vaccine efficacy is not possible as COVID-19 was less prevalent, and variants had not developed during mRNA vaccine trials. WHO indicates World Health Organization.

protein vaccine NVX-CoV2373 yet to be determined. mRNA-1273 has exhibited a range of increased incidence over controls, while BNT162b2 has been associated with increased risk in some but not all studies. In this report, we will emphasize studies that (1) through tracking registries or standard electronic medical records have the potential for high event capture as well as determination of disease specificity, (2) include unvaccinated control populations; (3) have robust identification and adjudication procedures for diagnosing suspected myocarditis. Data from 6 such studies^{64–69} are given in Table S1, with 3 of them having the advantage of also determining the COVID-19 infection myocarditis rate in the same parent populations. In addition to generally meeting these inclusion criteria, each of the studies also provides unique information.

Based on data presented in Table S1 as well has additional studies, there are 4 main variables that influence the risk of developing myocarditis/myocardial injury associated with receiving a COVID-19 vaccine. These are (1) the type of vaccine; (2) vaccinee age; (3) vaccinee sex; and (4) dose number (first or second for the initial vaccination). The 2 widely used mRNA platform vaccines, BNT162b2 and mRNA-1273, have clearly been shown to confer a small but increased risk of myocarditis that exceeds background rates (Table S1). For BNT162b2 in males and females in

age groups from 12 years and up the myocarditis or myopericarditis absolute incidence per 100 000 vaccinated persons ranges from 0.25⁶⁹ to 9.3⁶⁶ vaccinated persons for the first dose, and from 0.53⁶⁴ to 11.3⁶⁶ for the second dose. If the combined risk of both doses is considered in the 6 studies in Table S1,^{64–69} the range is 1.08⁶⁴ to 20.6⁶⁶ with a median (Q1–Q3 percentile) of 1.93 (1.21–7.31). For excess cases above control, where calculated in the data in Table S1 the values for BNT162b2 range from 0.10⁶⁴ to 0.42⁶⁶ for dose 1, and 0.76⁶⁶ to 9.16⁶⁷ for dose 2. For the combined dose 1 plus dose 2, the excess number of myocarditis including myopericarditis is a median of 1.21 (1.18–5.49)^{66–68} cases per 100 000 persons.

For mRNA-1273, the crude myocarditis/myopericarditis incidence in the 4 studies in which it could be calculated^{64–66,68} was a median pf 3.48 (2.27–7.68) per 100 000 persons, with an excess number of cases over control of 1.88 (1.60–5.84). In the 4 studies in which there was enough administration of mRNA-1273 to compare to BNT162b2, the myo/myopericarditis incidence was higher for mRNA-1273 in three^{64,65,68} and higher in males in the other⁶⁶ (Table S1). One of the studies listed in Table S1⁶⁸ directly compared the 2 mRNA vaccines incidence rate ratios and found a 1.6-fold higher rate for mRNA 1273 including data for doses 1 and 2, with an excess number of cases versus controls of 0.8.

Thus, for the general population ≥ 12 to 16 years age, the first course of 2 doses for BNT162b2 and mRNA 1273 are associated with respective crude incidences of myocarditis over control by an extremely small amount of approximately 2.0 and 3.5 cases per 100 000 persons, with an excess over control of 1.2 and 1.9 per 100 000. However, for both mRNA vaccines, the incidence exceeds the background myocarditis rate, with a greater myocarditis incidence after the second dose versus the first. These observations have also been applied to meta-analyses^{70,71} that include studies that do not meet the inclusion criteria in Table 1, with similar conclusions. The apparent slightly higher myocarditis rate of mRNA-1273 versus BNT162b2 may be due to its higher dose (100 versus 30 μ g) or some unknown difference in the 2 formulations.

Although there are only rare reports of myocarditis following adenovirus vector vaccines,^{72,73} the Patone et al study⁶⁴ identified an increased risk associated with the first dose of ChAdOx1 vaccine in subjects ≥ 16 years age (Table S1). However, there was no increased risk with dose 2, and no increased risk in persons < 40 years age. The inactivated virus vaccine CoronaVac has been widely used in China and elsewhere and has had only rare reports of myocarditis.⁶⁹ In a case-control study, CoronaVac's myopericarditis rate was not higher than controls, in contrast to BNT162b2's rate that exceeded controls after dose 2 and for doses 1 and combined⁶⁹ (Table S1). For NVX-CoV2373/Nuvaxoid recombinant S1 protein vaccine, there is a case report of myocarditis after administration,⁷⁴ and myocarditis was also reported in 4 cases out of 40 000 vaccine recipients in Phase III trials where it occurred only in men and within 10 days of vaccine receipt.⁷⁵ Novavax released a statement June 3, 2022, that the rate of myocarditis was balanced between the vaccine and placebo arms (0.007% and 0.005%), and there is insufficient evidence to establish a causal relationship.⁷⁶ However, the FDA review of the Novavax vaccine Phase 3 trials identified 5 cases of temporally related myocardial injury that clinically could have been myocarditis plus 1 case of pericarditis versus 1 case of possible myocarditis in the placebo arm that was 72 days post-vaccination.⁷⁷ Their conclusion was that the events of myocarditis/pericarditis are concerning for a causal association with NVX-CoV2373.

Data in Table S1 also demonstrate a higher incidence of myocarditis in males of all ages compared to females, ranging in BNT162b2 for the ≥ 12 to 16 years categories from 2.1⁶⁴ to 9.1⁶⁷ fold for dose 1 and 1.2⁶⁵ to 8.3⁶⁷ fold for dose 2. For mRNA 1273, there were not enough data to analyze a sex difference after dose 1, but the male:female incidence rates were 3.2⁶⁵ and 7.5⁶⁶ fold higher in males after dose 2. The higher incidence and excess cases of myocarditis in males vs. females is observed throughout the age range.^{66,67} (Table S1). For males, there is a striking inverse relationship between

age and myocarditis incidence or excess cases, for both mRNA vaccines.^{66,67} For BNT162b2, in the Mevorach et al⁶⁷ study for dose 2, the incidence increases from 1.74 in the ≥ 30 years group to 15.1 per 100 000 in the 16 to 19 years age band, with excess cases moving from 2.9 (1.98–4.09) to 13.6 (9.30–19.2). For mRNA 1273, the pattern is less clear, but in the Karlstad et al study,⁶⁶ the number of excess myocarditis cases/100 000 persons for dose 2 in the youngest age band (16–24 years) is 18.39 (9.05–27.72) versus 8.55 (6.40–11.41) in the entire ≥ 12 years age range. For females, the same age-related pattern is observed for BNT162b2 albeit with a much lower incidence,⁶⁷ which for mRNA 1273⁶⁶ precludes detection of an age-related pattern.

In addition, Table 3 gives data from the CDC and FDA co-managed VAERS passive surveillance system,⁷ which was the first U.S. database to alert health care providers to the increased risk of myocarditis among young males. Although VAERS likely under-reports cases, because of data quantity it is useful for identifying differences in subgroups.⁷⁸ There is an increased risk of myocarditis above estimated background rates following BNT162b2 dose 1 in males from 12 to 24 years age, and from age 5 to 49 years with dose 2. In contrast, females have an increased myocarditis risk only associated with dose 2, from 12 to 29 years age. In addition, consistent with the data in Table 1, in these risk bands, the observed rates in males are 4 to 11 times higher than in females.

Despite a higher incidence of myocarditis, the risk:benefit of mRNA vaccines is low in adolescents and young adults, especially when considering severity of illness.⁷⁹ Mild severity of illness and complete recovery is nearly universal in vaccine-induced myocarditis in children and young adults.^{8,64,80–82} Postacute sequelae of SARS-CoV-2 infection are also prevented.⁸³ However, most risk:benefit calculations do not include risk of multisystem inflammatory disorder associated with SARS-CoV-2 infection in children (multisystem inflammatory syndrome in children [MIS-C]) and its high severity of illness.^{84,85} Vaccination reduces the risk of acquiring MIS-C by 91%, and if acquired, the risk of requiring ICU admission in addition to the probability of needing life support.⁸⁶ Although MIS-C with a high percentage (83%) of cardiac involvement has been reported following mRNA vaccination, the incidence in children aged 12 to 17 years (0.29 [0.15–0.51] per 100 000 persons) is <3.0% of that with COVID-19 infection (11.3 [9.5–13.5]) and the clinical course is much more benign.⁸⁷ There are no reports of myocarditis or recurrent MIS-C in children vaccinated after an episode of MIS-C.⁸⁸ MIS has also been reported in adults (MIS-A) following COVID-19 infection or mRNA vaccines, but its incidence is much lower than in children.⁸⁹

No cases of myocarditis have been reported in vaccinated 0.5- to 5-year olds.⁹⁰ Therefore, ongoing vaccination in this age group should prevent not only vaccine and infection induced myocarditis, but also MIS-C.

Table 3. VAERS* Data as of May 28, 2022 on Myocarditis Following mRNA Vaccine Administration (per 100 000 Doses Administered)

Vaccine	Age, y	0–7 days		0–7 days		8–21 days		8–21 days	
		Males		Females		Males		Females	
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
BNT162b2	5–11	0.02	0.26	0.02	0.07	0.06	0.0	0.02	0.0
	12–15	0.53	4.64	0.07	0.41	0.12	0.12	0.04	0.02
	16–17	0.72	7.59	0.0	0.75	0.17	0.32	0.07	0.04
BNT162b2 and mRNA-1273	18–24	0.42	3.89	0.06	0.40	0.11	0.22	0.02	0.07
	25–29	0.18	1.52	0.04	0.35	0.04	0.11	0.02	0.0
	30–39	0.19	0.75	0.06	0.09	0.04	0.08	0.03	0.08
	40–49	0.05	0.33	0.04	0.16	0.02	0.05	0.02	0.0
	50–64	0.05	0.07	0.06	0.05	0.02	0.03	0.02	0.0
	≥65	0.02	0.03	0.01	0.05	0.03	0.02	0.01	0.01

*Vaccine Adverse Event Reporting System, a US CDC and FDA passive surveillance system. Shaded areas indicate reporting rate exceeded estimated background incidence. Table is extracted from a report by Shimabukuro T to the CDC's Advisory Committee on Immunization Practices on June 23, 2022 based on surveillance through May 28, 2022.⁷ Report includes 51.0 million total doses of BNT162b2 (27.7 first dose, 23.3 million second dose), 1,865 million doses of mRNA-1273 (950 608 first dose, 914 745 second dose) in children 5 to 17 years age, who had 635 myocarditis cases meeting the CDC definition reported.

Three of the studies listed in Table S1 also report the myocarditis rate from SARS-CoV-2 infection in the same vaccinated and control populations in which BNT162b2 and mRNA-1273 myocarditis rates were measured. In the Patone et al study,⁶⁴ the incidence of myocarditis associated with COVID-19 infection was 4.42 cases per 100 000 infected individuals of either sex and ≥16 years age, and 1.29 per 100 000 in those aged <40 years (Table S1). The incidence rate ratio in COVID-19 versus the background rates of myocarditis for the ≥16 years old controls was 9.76.⁶⁴ In Husby et al,⁶⁵ the COVID-19 myocarditis rate was 2.09 times background in the ≥12 years old group. For the Karlstad et al,⁶⁶ in the entire age range of ≥12 years, the myocarditis incidence was 56.8 cases per 100 000 in males and 43.7 per 100 000 in females, with respective fold increases over background myocarditis rate of 3.96 and 3.08 and a median (minimum, maximum) of 3.5. For the 3 studies in which mRNA vaccine and COVID-19 infection-associated myocarditis rates were measured,^{64–66} the COVID-19 rate is 3.52 (2.09–9.76) per 100 000 persons. This compares to a BNT162b2 dose 1, 2 IRR median fold increase over control of 1.48 (1.30–1.56) and an mRNA-1273 IRR of 6.25 (3.86–6.40). If the 3 studies in Table S1 that did not include a COVID-19 myocarditis incidence are included in the BNT162b2 and mRNA IRRs, the respective median (Q1, Q3 percentile) values are 2.47 (1.44–4.41) and 6.32 (4.46–8.49). Thus, when myocarditis risk in SARS-CoV-2 infection and mRNA vaccines are compared, including in the same studies to the same controls using the same methodology, the increased incidence rates compared to background are similar, with the median values for BNT162b2 (1.48 [N=3] or 2.47 [N=6]) and mRNA-1273 (6.25 [N=3] or 6.32 [N=4]) bracketing COVID-19 (3.52 [N=3]).

Clinical Course

In the case of myocarditis related to COVID-19 mRNA vaccination, symptom onset occurs approximately 2 days after vaccination and more commonly after the second dose, with 92% of patients reporting symptoms within 7 days. Clinical courses tend to be relatively mild, and although in a 323 person cohort 96% of patients were hospitalized, 95% had been discharged at the time of case review and none died.⁹¹ In Karlstad et al,⁶⁶ post-vaccine myocarditis was associated with 0.2 (0–0.4)% mortality rates within 28 days of the second dose of BNT162b2, compared with 0.8 (0.3–2.0) in unvaccinated control myocarditis cases. However, for mRNA-1273, in the 28 day window following the second dose the mortality was 4.5 (0.0–13.2). Further evidence that BNT162b2 is associated with a low mortality was provided by a Hong Kong population study where, in a 180 day follow-up period, the control, pre-COVID-19 myocarditis mortality rate was 11% compared with only 1% following BNT162b2 vaccination.⁷⁹

The inclusion of COVID-19 myocarditis in some of the SARS-CoV-2 vaccine myocarditis studies offers an opportunity to directly compare morbidity and mortality of these 2 disorders. In Husby et al,⁶⁵ vaccination was associated with a markedly reduced adjusted hazard ratio for death or cardiac arrest in the 28 days following administration compared with the unvaccinated control cohort, 0.51 (0.49–0.53) for the 2 doses of BNT162b2 and 0.41 (0.37–0.46) for mRNA-1273. In contrast, SARS-CoV-2 myocarditis was associated with an increased adjusted hazard ratio in the 28 days following infection, 13.64 (12.94–14.38), compared with uninfected controls. However, these data obviously include the ability of mRNA vaccines to reduce SARS-CoV-2 infection and

severe complications including death in the early periods post-vaccination,^{92,93} rather than directly demonstrating differences in the clinical courses of myocarditis associated with infection or vaccination.

Histopathology

The clinical course of COVID-19 vaccine-associated myocarditis has generally been mild and transient, and the role for EmBx characterization of histopathology has been limited.⁹⁴ In series in which EmBx has been performed,^{29,95} most cases have been negative for full evidence of inflammatory infiltrate or histologic myocarditis as defined by the Dallas Criteria.^{10,11} As with EmBx for myocarditis of other etiologies, this has been attributed to sampling error, as well as the possibility of other mechanisms leading to myocardial injury including evidence of low-level inflammatory response in this setting.^{29,72,96,97} However, several EmBx or autopsy histologic findings of vaccine-associated myocarditis have demonstrated an inflammatory infiltrate composed predominantly of lymphocytes and macrophages, with occasional eosinophils and even giant cells; some reports also note the presence of interstitial edema and neutrophils (Figure 4A and 4B).^{67,94,98,100–103} Immunohistochemically, a preponderance of T-lymphocytes has been highlighted by CD3 immunostaining, in some cases admixed with CD68-positive macrophages. As with lymphocytic myocarditis, B-lymphocytes have been less common in the infiltrate.^{98,101–103} PCR and serologic tests are typically negative for SARS-CoV-2 as well as other viruses at the time of diagnosis, excluding other etiologies for the histologic findings. In addition, some cases of COVID-19 vaccine-associated myocardial injury not meeting full Dallas Criteria^{10,11} may be considered borderline myocarditis histologically. The finding of scattered eosinophils in some cases differs from lymphocytic or viral myocarditis. Eosinophils are generally not seen in myocarditis from other viral etiologies, nor are they a common finding in COVID-19 myocarditis. However, rare cases of eosinophilic myocarditis and acute necrotizing/fulminant eosinophilic myocarditis (Figure 4C) with subsequent demise have been reported following COVID-19 vaccination, raising the possibility of a hypersensitivity reaction in response to vaccine contents.^{99,104–107}

As for other forms of suspected myocarditis, etiologies other than an inflammatory condition should be considered for mRNA vaccine-associated myocarditis when inflammation is not associated with myocardial injury. COVID-19 has shown a propensity for thromboembolic events, and multiple studies have also demonstrated this phenomenon associated with COVID-19 vaccination. Microthrombi affecting the heart tend to be identified in small vessels (Figure 4D through 4F) and were in some instances associated with hemorrhage (Figure 4G) or ischemic changes.^{29,108,109} In all these situations, evidence

of inflammatory infiltrate was absent, despite the clinical presentation and imaging being consistent with myocarditis.

Ultrastructural examination in cases of COVID-19 vaccine myocarditis has been infrequent. However, electron microscopy has demonstrated damaged myocytes adjacent inflammatory cells.⁹⁸ In our experience, the ultrastructural findings of COVID-19 vaccine-associated myocarditis have been mostly nonspecific, and features of cellular injury have been relatively minor. To our knowledge, only 2 studies have included electron microscopy findings of microthrombi within the heart (Figure 4F).^{39,108} Platelets and fibrin were identified within vessels, with varying degrees of occlusion, though most thrombi were nonocclusive. One of our cases documented an unusual accumulation of cell debris and organelles within interstitial areas (Figure 4H and 4I), indicative of cellular damage, though the damaged myocytes were not contained within the evaluated areas.²⁹ This finding provides evidence that myocardial damage is indeed occurring, though the cause of that damage is uncertain in this situation.

Imaging

Cardiac MRI

Reports on specific findings in COVID-19 vaccine by CMR are limited, we have reported 6 post COVID mRNA vaccination apparent myocarditis cases with clinical features including chest pain and shortness of breath, who had T2 hyperintensity and LGE findings.²⁹ Our and most other cases have also had markedly elevated serum troponin, CMR findings consistent with myocarditis, and normal coronary angiography. We also performed EmBx in 4 of our 6 cases, where the only findings were rare instances of microvascular thrombosis including on electron microscopy in 1 subject, and nonspecific changes in the other 3.²⁹ In addition, although the subject with microvascular thrombosis had an elevated CRP on admission, multiple other proinflammatory biomarkers drawn at the time of EmBx were within normal limits at a time when the patient had ongoing chest pain and subsequently had a persistently positive CMR suggestive of possible myocarditis.²⁹ Other cases have been reported where CMR findings were suggestive of myocarditis, but EmBx biopsy did not demonstrate an inflammatory infiltrate.^{72,97}

Chelala et al¹¹⁰ reported a group of adolescent patients undergoing CMR for suspected myocarditis following mRNA vaccine administration. CMR showed both EGE and LGE in 5 patients presenting with chest discomfort, elevated troponin levels and ECG abnormalities. The LGE images revealed 4 with subepicardial enhancement; and 1 with mid-to-subepicardial enhancement. All patients showed involvement of the inferior, inferolateral, or anterolateral walls. Quantitative criteria included T2 parametric mapping and quantification of myocardial signal intensity ratios (myocardium: skeletal muscle). In a

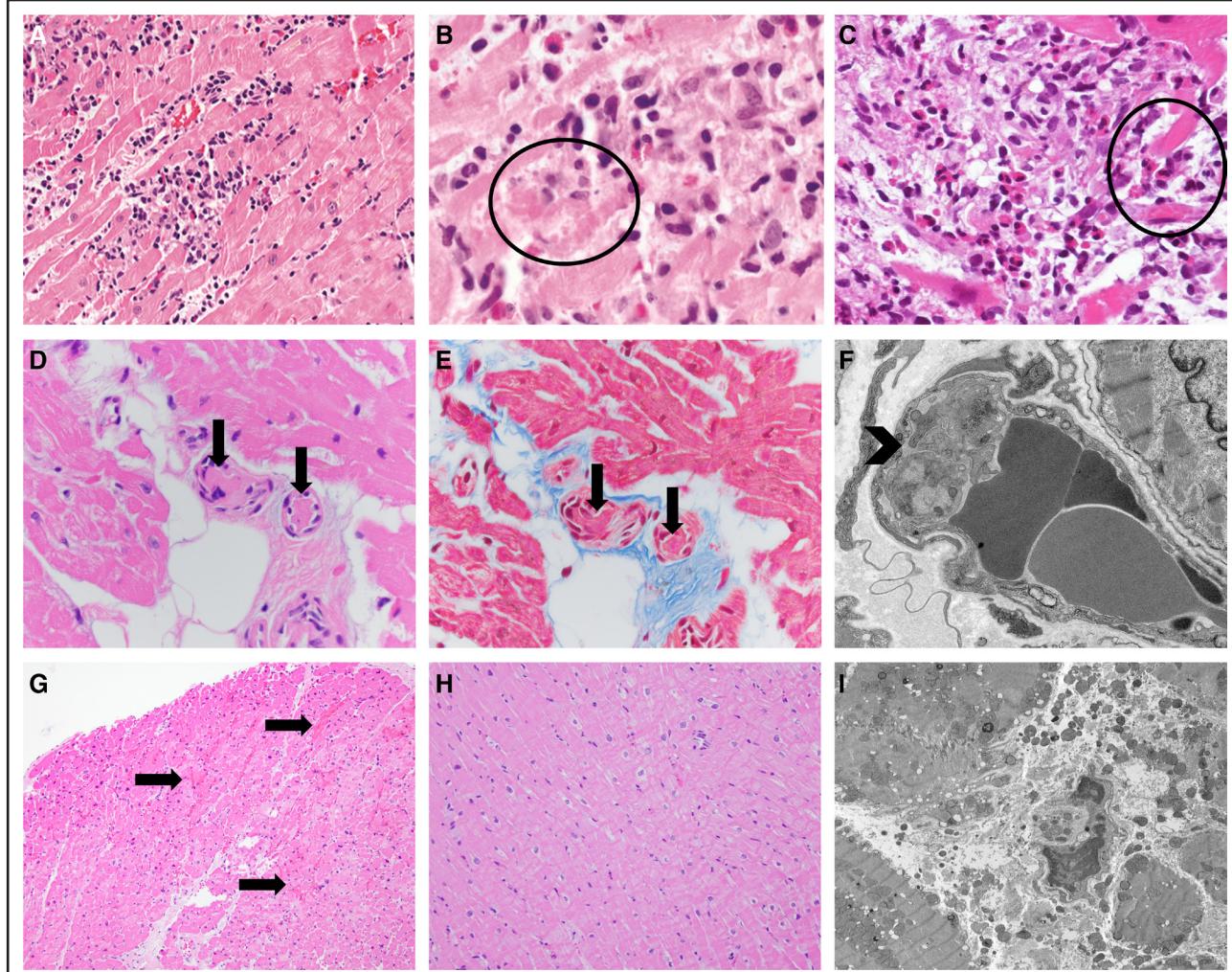


Figure 4. Endomyocardial biopsies from clinically diagnosed postvaccination myocarditis with an mRNA-based vaccine.

A, Myocarditis, histologically confirmed (H&E, 400 \times) from study by Verma et al.⁹⁸ **B**, Myocarditis with associated myocyte damage (H&E, 600 \times), from study by Verma et al.⁹⁸ **C**, Necrotizing eosinophilic myocarditis following vaccination (H&E, 400 \times), from study by Kimura et al;⁹⁹ circles highlight areas of myocyte damage. **D**, Microvascular fibrin thrombi (arrows) following mRNA vaccination, without evidence of inflammation (H&E, 600 \times , from study by Altman et al²⁹). **E**, Trichrome stain highlighting microvascular thrombi (600 \times).²⁹ **F**, Electron micrograph from patient in **D** and **E**,²⁹ demonstrating platelet-rich thrombus partially occluding a capillary (arrowhead). **G**, Intramyocardial hemorrhage (arrows) following mRNA vaccination, without evidence of inflammation (H&E, 100 \times). **H**, Normal appearing myocardium in patient clinically diagnosed with myocarditis following mRNA vaccination (H&E, 200 \times). **I**, Electron micrograph from patient H showing extracellular organelles and debris, suggestive of prior myocyte damage/resolving myocardial process.

17-year-old boy, basilar T2-mapping was abnormal and a 19-year-old male had a T2 signal intensity ratio of >3.0 . Two patients showed elevated segmental T1 relaxation times; one of these also exhibited elevated segmental T2 relaxation times. T2-weighted sequence hyperintensity is suggestive of edema which corresponded with areas of EGE and LGE on postcontrast imaging. Three patients exhibited a trace pericardial effusion, and 2 patients exhibited a small pericardial effusion without LGE. Based on Lake Louise Criteria,⁶ the CMR data were consistent with myocarditis in all 5 patients. These findings were similar to the cases we reported of focal/punctate regions of either T2 hyperintensity suggesting edema and or punctate regions of LGE,²⁹ as well as to

other studies.^{111,112} CMR abnormalities consistent with myocarditis associated with mRNA vaccine administration improve over the subsequent several months,^{29,113} but LGE may not completely resolve, suggesting the presence of residual fibrosis.¹¹³

Echocardiography

In Mevorach et al,⁶⁷ 48 of the 54 mRNA vaccine myocarditis patients had echocardiography performed. Left ventricular function was normal in 71% of the patients, while LV dysfunction was mild or moderate in 25%, and moderate to severe or severe in only 4%. In a cross-sectional study by Ilonze and Guglin,¹¹³ echocardiography was performed in 238 patients with clinically diagnosed

myocarditis following mRNA vaccination. Systolic function by LVEF was normal in 69%, while 22% had mild, and 3% had moderate or severe LV dysfunction. In our own vaccine myocardial injury series,²⁹ of 5 subjects who had no history of myocardial dysfunction 4 had an LVEF >55%, and the other whose LV function was presumably normal prior to myocarditis had moderate LV dysfunction with an LVEF of 37%. Thus, LV function as measured by LVEF is usually normal or only mildly impaired in mRNA vaccine-associated myocardial injury.

Positron Emission Tomography and Computerized Tomography

Combined ¹⁸F fluorodeoxyglucose positron emission tomography and computerized tomography has been used in the setting of COVID-19 myocarditis to diagnose myocardial inflammation¹¹⁴ and has recently been applied to vaccine myocarditis.^{115,116} The potential advantage over CMR is that it can quantify the degree of inflammation and can be used to serially monitor the disease process over time as well as the response to anti-inflammatory agents.

Are There Imaging Differences Between Myocarditis/Myocardial Injury From Post-Vaccination Versus COVID-19 Infection?

Cardiac Magnetic Resonance Imaging

Currently, there is no direct comparison of early or late follow-up CMR characteristics between SARS-CoV-2 infection- and vaccine-associated myocarditis/myocardial injury. Interestingly, both our report²⁹ and others^{111,112} note punctate or patchy, very focal regions of either T2 edema signal or LGE in patients with presumed vaccine-related myocarditis, whereas infection-associated myocarditis tends to be more linear mid-myocardial and subepicardial with/without pericardial involvement. In addition, reports suggest that vaccine-associated suspected myocarditis is not as persistent on follow-up imaging¹¹⁷ and tends to be less severe.

Echocardiographic Findings

Strain imaging of both left and right ventricle is a more sensitive way of detecting myocardial involvement rather than is standard 2D volumes and EF measurement. LV global longitudinal strain is reduced in the majority of COVID-19 myocarditis patients,¹¹⁸ and based on CMR studies RV strain is often abnormal in post-mRNA vaccination myocarditis.¹¹⁷ These sensitive measures of LV and RV systolic function thus have promise in identifying patients with myocardial injury. The RV is involved more frequently in COVID-19,¹¹⁹ at least in part due to the presence of pulmonary involvement from either infection or thromboembolic phenomena. Typically, in COVID-19-associated myocarditis, LV dysfunction resolves within a few months while reduction in RV systolic function may persist longer.

Pathophysiologic Mechanisms

The mechanisms producing myocardial injury following administration of an mRNA COVID-19 vaccine are not well understood. Possible explanations include altered gene expression, direct immune activation by mRNA, molecular mimicry, immune dysregulation, and aberrant cytokine expression.

Myocarditis after COVID-19 vaccination is in the range of very rare as a complication, and there is a paucity of data concerning endomyocardial tissue pathology. We compared the histopathology and gene expression changes of 7 patients with myocardial injury after COVID-19 infection versus 4 with myocardial injury after mRNA vaccination.²⁹ There was no evidence of an inflammatory infiltrate on myocardial biopsy in the postvaccine myocardial injury patients. However, compared with the COVID-19 infection myocardial injury patients, postvaccine subjects exhibited similar degrees of downregulation of the mRNAs for ACE2 and ITGA5, as well as upregulation of ACE and tissue factor (*Factor 3*, the initiator of the extrinsic pathway of coagulation; Figure 5).²⁹ After mRNA translation and extracellular release, S protein can bind with high affinity to its cognate receptor, ACE2, in the same manner as the SARS-CoV-2 virion. The marked myocardial downregulation in mRNA expression of ACE2 and its co-receptor ITGA5²⁹ after myocardial injury from both COVID-19 and mRNA vaccination suggests that the myocardium was exposed to high levels of S-protein, which then internalizes with ACE2 and induces pathological changes in gene expression and possibly other mechanisms of cytotoxicity. Decreased ACE2 and increased ACE enzyme levels would ultimately produce higher myocardial angiotensin II concentrations, triggering inflammation, coagulation, and myocardial dysfunction.²⁹ Increased tissue factor levels would be expected to further contribute to a procoagulant state. This scenario places Spike protein at the center of both COVID-19 infection and vaccination myocardial injury,^{29,120} and if confirmed this non-immune mechanism would open new avenues of research for preventing or mitigating myocardial damage from both SARS-CoV-2 and mRNA vaccines. Support for this hypothesis was recently provided by the report of circulating free Spike protein levels present up to 3 weeks post-vaccination in adolescents and young adults with myocarditis, compared to no detection of Spike in controls.¹²¹

Although previous reports have suggested that the risk of myocarditis during COVID-19 illness is estimated to be 100-fold greater than the risk of myocarditis from a COVID-19 mRNA vaccine,¹²² as described in the Incidence Section, studies listed in Table S1 indicate a similar incidence between myocarditis occurring in COVID-19 infection and after mRNA vaccines. The 1 common factor between infection and vaccination is the exposure to Spike protein, which has proved toxic in

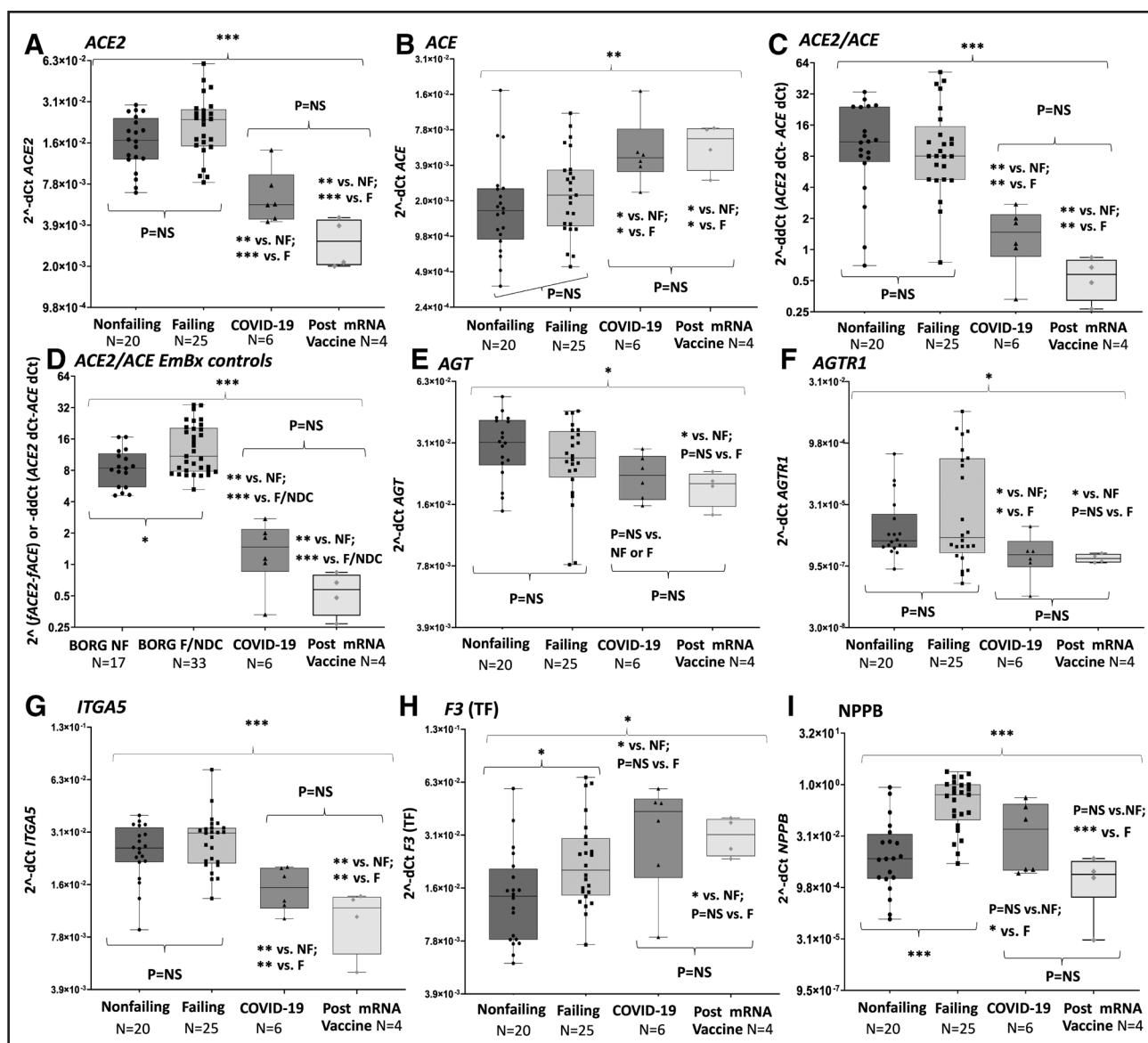


Figure 5. Box and Whisker plots for mRNA abundance as 2^{-dCt} referenced to GAPDH, median (Q1–Q3) for explanted heart nonfailing interventricular septum (IVS; nonfailing [NF], N=20), failing IVS (failing [F], N=25 [15 nonischemic dilated cardiomyopathy, 10 ischemic cardiomyopathy]); 17 endomyocardial biopsy (EmBx) nonfailing controls, 33 EmBx failing nonischemic cardiomyopathy (NDC) controls, 6 EmBx COVID-19 subjects (median [Q1–Q3]), and 4 EmBx postvaccine myocardial injury subjects.

ACE2/ACE from BORG study is calculated from microarray fluorescence units (δ) that are log₂-transformed. Significance levels are given above or below box plots as * $P<0.05$, ** $P<0.01$, *** $P<0.001$, P≥0.050. Reprinted from Altman et al²⁹ with permission from Elsevier and JACC: Basic to Translational Science. ACE indicates angiotensin I converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II receptor type 1; E2, angiotensin converting enzyme 2; ITGA5, integrin alpha 5; F3, factor 3; NS, nonsignificant; NPPB, natriuretic peptide B; and TF, tissue factor.

multiple studies.^{123–125} Genetic variation among individuals is a distinct possibility for the rare and unpredictable nature of post vaccine myocarditis. It has been hypothesized that persons with underlying genetic susceptibility can experience aberrant immune activation and cytokine production during infection with SARS-CoV-2.¹²⁶ Aberrant immune activation triggered directly by mRNA molecules could also contribute to myocardial inflammation by triggering cytokine release and a general inflammatory response. Modification of ribonucleoside bases in the

mRNA used in vaccines is thought to reduce signaling by Toll-like receptors, thereby reducing innate immune response to the mRNA.⁵⁶ However, direct immune activation by mRNA would be expected to produce a systemic inflammatory response with involvement of multiple organ systems, and this type of generalized response has not been associated with mRNA vaccines. Moreover, emerging data indicate that the risk of myocarditis after the Novavax recombinant spike protein vaccine and mRNA vaccines may be similar,⁷⁷ and a similar increased

risk of myocarditis after both protein and mRNA-based vaccines does not support mRNA-induced immune activation as a major mechanism of vaccine-associated myocarditis. However, genetic variation in ACE2 leading to differences in Spike protein binding affinity¹²⁷ would explain a similar degree of infrequent myocarditis between mRNA and Spike protein-based vaccines.

Molecular mimicry with immunological cross reactivity between spike proteins and self-antigens may also contribute to myocarditis following mRNA vaccines. Spike protein antigen may cross-react with human α -myosin,¹²⁸ an important sarcomeric protein involved in regulation of contractile function, although this can rarely lead to autoimmune reactions.^{129,130} The cross-reaction, however, may trigger a proinflammatory cascade, with dysregulated activation of B cells in at-risk individuals.¹²⁶

Differences in sex hormones may explain why young males are more likely to develop vaccine-associated myocarditis than females. By stimulating ACE2 expression¹³¹ or activating a TH1 response¹³² and inhibiting anti-inflammatory cells,^{133,134} testosterone may contribute to myocarditis development. Furthermore, estrogen can inhibit proinflammatory cells.^{135,136} These hormonal differences may explain the increased risk of myocarditis among males compared with females and among adolescents or young adults compared older adults and preadolescent children.

Other putative hypothesis about the pathophysiology of myocarditis after COVID-19 vaccination have less support. For example, while allergic mechanisms have been proposed, myocarditis after COVID-19 vaccination is rarely associated with a systemic hypersensitivity reaction or evidence of eosinophils on myocardial biopsy.¹³⁷ Similarly, LNP or adjuvants have not linked been linked to allergic reactions. There also has been no evidence that vaccine induced cellular or humoral immunity leads to enhancement of SARS-CoV-2 infection in immunized persons,¹³⁸ and prior cases of vaccine-induced myocarditis were not associated with an antecedent or concurrent acute SARS-CoV-2 infection.²⁹

Mitigation Strategies

Multiple mitigation strategies have been proposed to prevent vaccine-related myocarditis. Pillay et al¹³⁹ reported that delaying the second COVID-19 vaccine dose beyond 30 days and prioritizing Novavax or Pfizer vaccine over Moderna in high-risk individuals may reduce risk. Creating a risk assessment calculator using age, sex, vaccine history, and predisposing conditions to guide decisions about the type, schedule, and dose of mRNA vaccinations could potentially provide risk-based guidance. Based on myocardial gene expression findings,²⁹ anticoagulation and aggressive angiotensin II inhibition could potentially provide benefit in selected cases of myocardial injury. Advances in the knowledge and

understanding of the underlying mechanisms related to COVID-19 vaccine-related myocarditis are essential, as it is likely that mRNA COVID-19 vaccines will continue to be an important tool for controlling the COVID-19 pandemic and possibly for the prevention of other infectious diseases. In view of the potential role Spike protein plays in both COVID-19 infection and postvaccine myocarditis and myocardial injury, it will be interesting if a non-Spike protein Ag-based vaccine¹⁴⁰ will carry the same risk for myocardial damage. In addition, the translated Spike protein receptor binding domain in vaccines could theoretically be modified to reduce ACE2 binding affinity without loss of immunogenicity, which would reduce S protein toxicity while maintaining vaccine effectiveness.

TREATMENT OF MYOCARDITIS

Unless otherwise stated, this section applies to viral non-COVID-19, SARS-CoV-19, and postvaccination myocarditis. In patients presenting with acute myocarditis and heart failure symptoms with reduced LV ejection fraction and stable hemodynamics, conventional therapies including diuretics, beta blockers, angiotensin/neprolysin inhibitors, and aldosterone antagonism should be initiated. The use of immunosuppression, typically initially consisting of corticosteroids, is debatable in this population. In general, immunosuppression should not be considered in suspected myocarditis unless the patient is exhibiting worrisome progressive myocardial dysfunction, a situation in which an EmBx should also be considered to document the presence of an inflammatory infiltrate that might be amenable to therapy.²⁰ In cases of myocarditis with preserved LVEF (HFpEF), there are insufficient data to determine whether traditional guideline-directed medical therapy is useful in preventing downstream negative cardiac remodeling and fibrosis.¹⁴¹

Patients who become hemodynamically unstable should be supported with intravenous inotropes, and those progressing to cardiogenic shock despite inotropes are candidates for mechanical circulatory support, potentially including intra-aortic balloon counterpulsation, percutaneous microaxial or rotary mechanical support devices, and veno-arterial extracorporeal membrane oxygenation. These types of support devices allow for ventricular unloading, systemic and coronary perfusion and venous decongestion in order to both support end-organ function and provide a bridge to recovery versus heart transplantation or durable left ventricular assist device (LVAD) implantation.¹⁴² Patients in this category should be managed in centers with expertise in advanced heart failure and cardiac transplantation. Patients with specified subtypes of myocarditis (giant cell, eosinophilic myocarditis) should be managed with targeted therapies and immunosuppression as indicated by published guidelines (Table 1) or referred to ongoing trials.¹⁴³

Patients with chest pain with preserved cardiac function and no ventricular arrhythmias can be managed in the outpatient setting with close follow-up. Those with definite myocarditis and mild-moderate severity illness should be hospitalized initially. In the context of SARS-COVID-19 infection, the spectrum of disease presentation remains broad. If patients have concurrent pneumonia with supplemental oxygen requirement and adults with multi-inflammatory syndrome, it is reasonable to utilize corticosteroid therapy.⁵ Pericardial involvement can be managed with NSAIDs and colchicine.¹⁴⁴ If patients progress to fulminant myocarditis with hemodynamic compromise, transfer to a shock center with expertise in advanced heart failure therapies is recommended for ongoing management, mechanical circulatory support and transplant evaluation.⁶ Similarly, patients presenting with chest pain, elevated troponins, abnormal ECG and CMR findings or hemodynamic instability following COVID-19 vaccination should be hospitalized for monitoring and stabilization. If symptoms improve quickly, supportive management is usually sufficient. For ongoing chest discomfort, troponin elevation and cardiac dysfunction, treatment with NSAIDs, colchicines, and corticosteroids can be considered. Following stabilization, patients should be initiated on guideline-directed medical therapy for heart failure. Avoidance of strenuous physical activity for 3 to 6 months should be stressed. Follow-up surveillance testing should be considered, including ECG, CMR, and echocardiogram, to evaluate cardiac recovery, inflammation, and fibrosis and to assess prognosis.

CONCLUSIONS

COVID-19 vaccines effectively reduce the risk of SARS-CoV-2 infection, hospitalization, death, and other complications of infection including myocarditis and postacute sequelae of COVID-19. While myocarditis is a serious adverse effect of the mRNA COVID-19 vaccines, the incidence is very low (1.2–1.9 excess cases per 100 000 persons vaccinated with the first 2 doses, above background myocarditis rate), and most cases recover quickly. The Advisory Committee on Immunization Practices, therefore, recommends all persons 6 months and older receive the COVID-19 vaccine as the benefits of COVID-19 vaccination outweigh the rare risk of myocarditis.¹⁴⁵ However, the long-term effects of even mild vaccine-associated myocardial injury are unknown, and resolved cases may exhibit some degree of permanent damage such as interstitial fibrosis. Therefore, measures to reduce the risk of myocarditis/myocardial injury should be implemented as they become identified and available. If myocarditis occurs, additional COVID-19 vaccines are generally avoided.¹⁴⁵ Most importantly, the mechanisms of myocarditis after an mRNA COVID vaccine are not understood and further research is needed to inform safer vaccine use.

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Disclosures

M.R. Bristow is an Officer and shareholder of ARCA Biopharma, a precision therapeutics biotechnology company developing pharmacogenetic heart failure drugs. The other authors report no conflicts.

Supplemental Material

Table S1

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