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Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults

Running Title: *Truong et al.; Suspected Myocarditis After COVID-19 Vaccination*

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Abstract

Background: Understanding the clinical course and short-term outcomes of suspected myocarditis following COVID-19 vaccination has important public health implications in the decision to vaccinate youth.

Methods: We retrospectively collected data on patients <21 years-old presenting before 7/4/2021 with suspected myocarditis within 30 days of COVID-19 vaccination. Lake Louise criteria were used for cardiac magnetic resonance imaging (cMRI) findings. Myocarditis cases were classified as confirmed or probable based on the Centers for Disease Control and Prevention definitions.

Results: We report on 139 adolescents and young adults with 140 episodes of suspected myocarditis (49 confirmed, 91 probable) at 26 centers. Most patients were male (N=126, 90.6%) and White (N=92, 66.2%); 29 (20.9%) were Hispanic; and median age was 15.8 years (range 12.1-20.3, IQR 14.5-17.0). Suspected myocarditis occurred in 136 patients (97.8%) following mRNA vaccine, with 131 (94.2%) following the Pfizer-BioNTech vaccine; 128 (91.4%) occurred after the 2nd dose. Symptoms started a median of 2 days (range 0-22, IQR 1-3) after vaccination. The most common symptom was chest pain (99.3%). Patients were treated with nonsteroidal anti-inflammatory drugs (81.3%), intravenous immunoglobulin (21.6%), glucocorticoids (21.6%), colchicine (7.9%) or no anti-inflammatory therapies (8.6%). Twenty-six patients (18.7%) were in the ICU, two were treated with inotropic/vasoactive support, and none required ECMO or died. Median hospital stay was 2 days (range 0-10, IQR 2-3). All patients had elevated troponin I (N=111, 8.12 ng/mL, IQR 3.50-15.90) or T (N=28, 0.61 ng/mL, IQR 0.25-1.30); 69.8% had abnormal electrocardiograms and/or arrythmias (7 with non-sustained ventricular tachycardia); and 18.7% had left ventricular ejection fraction (LVEF) <55% on echocardiogram. Of 97 patients who underwent cMRI at median 5 days (range 0-88, IQR 3-17) from symptom onset, 75 (77.3%) had abnormal findings: 74 (76.3%) had late gadolinium enhancement, 54 (55.7%) had myocardial edema, and 49 (50.5%) met Lake Louise criteria. Among 26 patients with LVEF <55% on echocardiogram, all with follow-up had normalized function (N=25).

Conclusions: Most cases of suspected COVID-19 vaccine myocarditis occurring in persons <21 years have a mild clinical course with rapid resolution of symptoms. Abnormal findings on cMRI were frequent. Future studies should evaluate risk factors, mechanisms, and long-term outcomes.

Key Words: COVID-19 vaccine, myocarditis, adolescents, young adults

Non-standard Abbreviations and Acronyms:

BNP = Brain natriuretic peptide
CRP = C-reactive protein
cMRI = Cardiac magnetic resonance imaging
ECG = Electrocardiogram
ECMO = Extracorporeal membrane oxygenation
HIV = Human immunodeficiency virus
HMPV = Human metapneumovirus
ICU = Intensive care unit
IVIG = Intravenous immunoglobulin
LVEF = Left ventricular ejection fraction
MIS-C = Multisystem inflammatory syndrome in children associated with COVID-19
NSAID = Nonsteroidal anti-inflammatory drug
PCR = Polymerase chain reaction
RCA = Right coronary artery
RSV = Respiratory syncytial virus
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2
VAM = Vaccine associated myocarditis
VT = Ventricular tachycardia

Clinical Perspective

What is new?

- Suspected myocarditis temporally related to COVID-19 vaccination has been reported in adolescents ≥12 years-old and young adults since the emergency use authorization of the Pfizer-BioNTech COVID-19 vaccine, particularly in male adolescents and young adults.
- While the majority of patients with suspected vaccine associated myocarditis have normal ventricular systolic function on echocardiogram, many have abnormal findings suggestive of myocarditis on cardiac MRI in the setting of elevated troponin and electrocardiographic changes.
- Ventricular arrhythmias and the need for inotropic/vasoactive medications were rare, and no patients died or required mechanical circulatory support.

What are the clinical implications?

- Despite laboratory and cardiac MRI evidence of myocardial injury, the majority of adolescents and young adults with suspected myocarditis following COVID-19 vaccination have rapid recovery of symptoms and mild clinical course.
- Further studies are needed to better understand the timing of resolution of myocardial injury, mechanism of myocardial injury, and long-term outcomes.

Background

Rare cases of myocarditis have been reported in adults[1-3] following COVID-19 vaccination in Israel[4] and in the US military,[5] with most cases occurring in males <30 years old. Since the authorization to administer the Pfizer-BioNTech COVID-19 vaccine in those as young as 12 years of age, suspected myocarditis temporally related to the vaccine has also been reported in adolescents.[6-8] Myocarditis has been associated with other vaccines, such as smallpox[9] and influenza,[10] though data are limited regarding symptoms, clinical course, and short-term outcomes of suspected myocarditis following COVID-19 vaccination. On June 23, 2021, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices reported a likely link between mRNA COVID-19 vaccination and myocarditis, particularly in those ≤39 years old.[11] We aim to describe a large case series of suspected myocarditis temporally related with the COVID-19 vaccine in adolescents and young adults <21 years old across the United States and Canada.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

We collected data retrospectively for adolescents and young adults <21 years old who presented with symptoms, laboratory markers, and/or imaging findings concerning for myocarditis within 30 days of COVID-19 vaccination from 26 pediatric medical centers across the United States and Canada prior to July 4, 2021. We included patients with clinically suspected myocarditis[12, 13] who had elevated troponin levels and abnormal electrocardiograms (ECGs), cardiac function on non-invasive imaging, or findings consistent with myocarditis on cardiac magnetic resonance imaging (cMRI), including myocardial edema or late gadolinium enhancement.[14] Cases of suspected vaccine associated myocarditis (VAM) were categorized as probable or confirmed using the CDC case definitions (Table 1).[11]

We excluded patients in whom troponin levels were not measured or had normal levels, or who had a plausible alternative etiology for suspected myocarditis. Evaluations for alternative etiologies were at the discretion of sites, based on local assessments (Supplemental Table 1). If a patient presented with symptoms and findings suggestive of myocarditis after more than one vaccine dose, the more severe presentation was added to the aggregate data for analysis. The study was approved by the Institutional Review Boards of each center and waivers of consent were granted.

Data Obtained

We collected de-identified and targeted demographic, clinical, laboratory, imaging and ECG, and short-term outcomes data. Prior COVID-19 infection was defined as having a personal history of laboratory-confirmed SARS CoV-2 testing and/or having had symptoms and immediate household family member(s) who tested positive for SARS CoV-2 but the patient was not tested. Left ventricular systolic function was categorized as normal if graded as normal by local assessment, or if left ventricular ejection fraction (LVEF) was ≥55%; mildly decreased systolic function was defined as LVEF <45-54%, moderately decreased if 35-44%; and severely decreased if <35%. The decision and the timing to obtain cMRIs were at the discretion of the local clinical teams, and cMRIs were performed using local protocols (Supplemental Table 2). Data on cMRIs were collected retrospectively from clinical reports.

Statistical analyses

Descriptive statistics include percentages for discrete variables and median values with range or interquartile range for continuous variables. Fisher's exact or Wilcoxon-Rank-Sum tests were used to compare markers of illness severity in patients who did vs. did not undergo cMRI, and time to cMRI in those that were normal vs. abnormal. Markers of illness severity included need for intensive care unit (ICU) stay, left ventricular dysfunction on echocardiogram, and troponin I levels, which were performed more frequently than troponin T. All analyses were performed using Stata 11.2 (College Station, TX)

Results

As of July 4, 2021, 146 episodes of clinically suspected VAM occurred in 145 adolescents and young adults <21 years old at 26 centers, with 6 patients excluded due to lack of abnormal troponin. Thus, 140 episodes in 139 patients were analyzed. One patient presented with suspected myocarditis following both doses of the Pfizer-BioNTech vaccine, with a more severe course after the 2nd dose; data from his 2nd episode are included in the aggregate analysis, as detailed below. The majority of patients were White (N=92, 66.2%), non-Hispanic (N=96, 69.1%), and male (N=126, 90.6%) with a median age of 15.8 years (range 12.1-20.3, IQR 14.5-17.0) (Table 2). Based on symptoms, laboratory and imaging data, 49 (35.0%) episodes of suspected myocarditis met criteria for confirmed myocarditis based on CDC classification, and the remaining 91 (65.0%) would be classified as probable. No patients underwent endomyocardial biopsy.

Of the 140 episodes of clinically suspected VAM, 124 (88.6%) were evaluated with SARS CoV-2 PCR testing at the time of presentation (Supplemental Table 1), all of which were negative. Two patients had positive PCR testing within 32 days of presentation of suspected myocarditis, and thus were not tested again. Fifteen (10.7%) patients had evidence of previous COVID-19 infection by history (N=5), positive nucleocapsid antibodies (N=5), or both (N=5). Prior COVID-19 infection occurred <1 month to up to 10 months before the suspected myocarditis episode in the 10 patients with a known history. The majority (N=94, 67.6%) had no history of prior infection and/or had negative nucleocapsid antibodies to COVID-19, though in 30 patients (21.6%) the history was unknown and no nucleocapsid antibody testing was performed (Table 2). Of the 12 patients who presented with myocarditis after the 1st dose of vaccine, six had a history of prior COVID-19 infection or had the presence of nucleocapsid antibodies. Evaluation for alternative microbial etiologies for suspected myocarditis varied (Supplemental Table 1), with no plausible alternatives determined by centers. None had a prior history of multisystem inflammatory syndrome in children (MIS-C).

Vaccination Data, Symptoms, and Clinical Course

The majority of patients with suspected myocarditis received mRNA vaccine, with 131 (94.2%) after the Pfizer-BioNTech and 5 (3.6%) after the Moderna vaccines. One case (0.7%) occurred after the Johnson and Johnson vaccine. The brand of vaccine was unknown in 2 patients. Patients presented more frequently after the 2nd dose (N=128, 91.4%). (Table 3). Onset of symptoms occurred at a median of 2 days (range 0-22, IQR 1-3) following vaccine administration, with 5 patients presenting with symptoms 7-20 days, and only 1 presenting with symptoms ≥21 days after vaccination. Chest pain was the most common symptom, occurring in 138 patients (99.3%). Fever and shortness of breath each occurred in 30.9% and 27.3% of patients, respectively (Table 3).

Although 26 patients (18.7%) were managed in ICUs, inotropic/vasoactive support was used in only 2 (1.4%): one patient was treated with epinephrine and norepinephrine, and the other patient was treated with milrinone. No patient required extracorporeal membrane oxygenation (ECMO). All patients survived. The median hospital length of stay was 2 days (range 0-10, IQR 2-3).

Most patients (N=113, 81.3%) were treated with nonsteroidal anti-inflammatory drugs (NSAIDs); 76 (54.7%) were treated with NSAIDs alone. Intravenous immunoglobulin (IVIG) was administered to 30 (21.6%) patients, with glucocorticoids also given to 30 patients (Figure 1). Glucocorticoid regimens varied, ranging from IV glucocorticoids alone (N=6) at doses of 0.5-10 mg/kg/day for 1-3 days, to oral glucocorticoids alone (N=2) at 0.5-0.67 mg/kg/day for 5-10 days, or IV and oral glucocorticoids (N=22) with a taper over 2-73 days. Colchicine was used in 11 patients (7.9%). Twelve patients (8.6%) had complete clinical improvement without any anti-inflammatory therapies.

Laboratory Data

All patients had elevated troponin I (median 8.12 ng/mL, IQR 3.50-15.90 ng/mL; N=111) or T (median 0.61 ng/mL, IQR 0.25-1.3 ng/mL; N=28) (Table 4). Median C-reactive protein (CRP) levels were mildly elevated (3.3 mg/dL, IQR 1.1-6.2 mg/dL; N=116). The median brain natriuretic peptide (BNP) level was within the normal range (55.0 pg/mL, IQR 18.9-147.0 pg/mL; N=101) and median NT-proBNP was mildly elevated (159 pg/mL, IQR 91.5-810.3 pg/mL; N=8) (Table 4).

ECGs and Arrhythmias

Electrocardiograms were obtained in 138 patients (99.3%), of which 97 (69.8%) were abnormal. The most common abnormal ECG finding was ST segment and/or T wave abnormalities/elevation (N=95, 97.9%) (Figure 2a), with low voltages also seen in some (N=5, 3.6%). Of the 5 patients with low voltages, 3 had normal voltages within 3.5 weeks; one did not follow-up with the contributing site, and thus no follow-up ECGs were available; one continued to have low voltages at 5.5 weeks. Occasional premature ventricular (N=3) or atrial (N=1) contractions, atrial tachycardia (N=1), first degree atrioventricular block (N=1), and complete heart block (N=1) were observed, though uncommon.

Non-sustained ventricular tachycardia (VT) occurred in seven patients (5.0%), either on ECG, telemetry, or on ambulatory monitoring. Six had normal LVEF on echocardiogram, and one had mildly decreased systolic function (LVEF=50%). Of the six patients with VT who underwent cMRI, all had late gadolinium enhancement and myocardial edema. Two patients were treated with NSAIDs alone, one with IVIG and NSAIDs, two with IVIG and glucocorticoids, one with glucocorticoids and NSAIDS, and one with IVIG, glucocorticoids, and NSAIDs; this last patient had a 15-beat run of non-sustained VT on a Holter monitor (Figure 2b) and was readmitted and treated with atenolol.

One patient presented to an emergency department with chest pain and was diagnosed with complete heart block. He was admitted to the pediatric ICU for monitoring, and no pacing was needed. Ventricular systolic function was normal on echocardiogram, and cMRI revealed late gadolinium enhancement without evidence of myocardial edema. This patient was treated with IVIG and steroids and his rhythm recovered within 24 hours of admission.

Cardiac Imaging

Echocardiography was performed in all patients. The majority (N=113, 81.3%) had normal systolic function, while 22 (15.8%) had mild, 2 (1.4%) had moderate, and 2 (1.4%) had severe dysfunction (Table 4). Twenty-five patients with LVEF<55% had recovery of systolic function to normal, with one patient awaiting outpatient follow-up at the time of this submission. Only one patient had a pericardial effusion, which was small. One patient had coronary artery dilation, with further details as noted below.

Initial cMRI was performed in 97 patients at a median of 5 days (range 1-88, IQR 3-17) after symptom onset, of whom 75 (77.3%) had abnormalities. Among patients with abnormal cMRIs, late gadolinium enhancement was noted in 74 (98.7%) and myocardial edema was present in 54 (72.0%) (Table 4, Figure 3). Among the 97 cMRIs performed, 76.3% and 55.7% had evidence of late gadolinium enhancement or myocardial edema, respectively, and 49 (50.5%) met Lake Louise criteria for myocarditis (Table 4, Supplemental Table 2). Of those with abnormal cMRIs, 62 (82.7%) occurred in patients with normal left ventricular systolic function on echocardiogram. Patients with vs. without a cMRI did not differ significantly with respect to ICU admission (24.1% vs. 16.7%, p=0.26), having ≥mild left ventricular systolic dysfunction (23.2% vs. 11.9%, p=0.17), or troponin I levels (9.18 vs. 5.03 ng/mL, p=0.08). Median days from symptom onset to cMRI were significantly shorter for patients with abnormal vs. normal cMRIs (4 vs. 24 days, p<0.01). However, six of the 15 cMRIs performed >30 days after symptom onset had findings at LGE (even at up to 88 days), while seven of the 22 normal cMRIs were obtained within 7 days of symptom onset.

Cases of Interest

A Patient with Suspected Myocarditis Following the 1st and 2nd Vaccine Doses

A 17-year-old White male with a history of obesity and hyperlipidemia and no known prior history of COVID-19 infection had presumed myocarditis after both the 1st and 2nd doses of the Pfizer-BioNTech vaccine. He had onset of chest pain 20 days after his first dose and presented to the emergency department; labs showed a peak troponin I of 0.45 ng/mL. No testing for acute or prior COVID-19 infection was performed, and no other etiologies for myocarditis were evaluated at that time. His ECG and echocardiogram were normal, and cMRI was not performed. He was treated with NSAIDs as an outpatient. His chest pain resolved, with decrease in troponin level to 0.3 ng/mL 3 days after presentation.

He received his 2nd dose of vaccine 10 days after presenting with his initial episode of suspected myocarditis following vaccination (*i.e.* 30 days after receiving his 1st dose of vaccine). Chest pain occurred 5 days after his 2nd vaccine dose, with a much higher peak troponin I level of 34.5 ng/mL. His ECG showed diffuse ST segment changes and non-sustained VT. Left ventricular systolic function was

normal. Cardiac MRI showed late gadolinium enhancement and myocardial edema. He was treated with IVIG and NSAIDs. Nucleocapsid IgG testing sent prior to IVIG was negative. Thyroid peroxidase antibody group and Sjogren syndrome-A antibodies were positive, but these were obtained after IVIG administration and he had no prior history of symptoms or findings suggestive of these disorders. He was hospitalized for 4 days, which included ICU admission, though no inotropic or vasoactive support was required.

Of note, he also had a history of suspected myocarditis at age 10 years, with symptoms of fever, sore throat, and chest pain. At that time, he was admitted to the ICU, with troponin I level of 0.78 ng/mL, normal ECG and normal function by echocardiography. No cMRI was performed associated with this episode.

A Patient with Suspected Myocarditis and Coronary Artery Dilation

A 16-year-old Black male who had COVID-19 infection 32 days prior to receiving his 1st dose of Pfizer-BioNTech vaccine had dilated coronary arteries on presentation with suspected VAM. He presented with chest pain 7 days after the 1st dose of vaccine; he had no fevers or other organ system involvement, and he did not meet CDC criteria for MIS-C[15] or American Heart Association criteria for complete or incomplete Kawasaki disease.[16] Peak CRP was 0.62 mg/dL and peak troponin I level was 17.5 ng/mL. Nucleocapsid antibody and spike antibody testing were positive. His ECG showed ST segment elevation. Telemetry showed ventricular ectopy for which he was started on metoprolol. He had no VT or other sustained arrythmias while in the hospital, but routine outpatient screening with a Holter monitor showed atrial ectopic tachycardia with rare atrial and ventricular ectopy (<1%). His echocardiogram at presentation showed an LVEF of 51% with a small aneurysm of the right coronary artery (RCA, Z-score of 3.8) and mild dilation of the left anterior descending coronary artery (Z-score of 2.2) (Boston Z-score system). The left main coronary artery Z-score was normal. He was treated with glucocorticoids and aspirin. On hospital day 3, the RCA Z-score had decreased to 2.6 and the left coronary artery dimensions and LVEF had normalized. One month later the RCA Z-score was 2.9, and it remained enlarged at his most recent evaluation 76 days after presentation. He has not yet received his 2nd dose of vaccine.

Discussion

In this large case series from North America, we describe 139 adolescents and young adults <21 years old who had 140 episodes of clinically suspected myocarditis temporally related to COVID-19 vaccination. The CDC case definition[11] of confirmed myocarditis following vaccination was met in 35%, with elevated troponin levels and cMRIs that met Lake Louise criteria for myocarditis, and the remainder met criteria for probable cases. Symptoms and clinical findings typically developed within a week of vaccination and occurred in most patients following the 2nd dose. Ventricular tachycardia and complete heart block were uncommon complications (5.8%) and occurred in the absence of ventricular systolic dysfunction in all but one in this series. Many patients (80.6%) had pseudo-infarct presentation with chest pain, ST changes on ECG, and elevated troponin with normal left ventricular systolic function.[17] In the <20% of patients with depressed LVEF on echocardiogram at presentation, systolic function normalized in all who had follow-up echocardiograms at the time of this submission. Though only 50.5% of cMRIs performed met Lake Louise criteria for myocarditis, findings of late gadolinium enhancement were seen in 76.3% and myocardial edema in 55.7% of all cMRIs performed. Over 80% of these abnormal cMRIs occurred in the setting of normal systolic function on echocardiogram. No patients died or required ECMO support, and nearly 1 in 5 patients were admitted to an ICU, though the use of inotropic/vasoactive support was rare. Similar to myocarditis patients with pseudo-infarct presentation,[12, 17, 18] most patients had a relatively benign clinical course. Longer term surveillance is needed, however, to determine the natural history of suspected myocarditis temporally related to COVID-19 vaccines.

The findings in our large case series of adolescents and young adults with clinically suspected myocarditis following COVID-19 vaccination add to previously reported, smaller case series and case reports.[6-8, 19-21] Our large series is similar to earlier reports in finding a predominance of White and non-Hispanic males, with symptoms typically within a week of the 2nd dose of mRNA vaccine and cMRI abnormalities seen frequently.[21] A unique feature of our series is a patient with episodes of myocarditis after both his 1st and 2nd doses of the Pfizer-BioNTech vaccine, though there are other features of this patient's clinical history that may make his case less generalizable. Nonetheless, the greater severity of

symptoms and lab findings in this patient after his second vs. first dose supports the consideration of withholding or deferring a second dose of mRNA COVID-19 vaccine in patients with suspected myocarditis after the first dose until more information is available.[22]

We also describe a patient with coronary artery involvement, which to our knowledge, has not been previously reported in patients with post-COVID-19 vaccine myocarditis. However, coronary artery dilation has been described in non-COVID-19 viral myocarditis[23] and in myocarditis in the setting of COVID-19 infection.[24] As this patient had COVID-19 infection 32 days prior to his vaccination, it is unclear if the coronary artery findings are related to the infection, the vaccination, a combination of the two, or completely unrelated. While the timing of his presentation and cardiac findings are similar to those that have been described in MIS-C, he otherwise did not meet CDC criteria for MIS-C. Coronary artery Z-scores, *i.e.*, coronary artery dimensions normalized for body surface area, have high inter- and intra-observer agreement in young children.[25] However, poor windows may limit the technical feasibility of coronary measurements in larger children and adolescents. Until more data are available, focused echocardiographic coronary artery imaging in patients presenting with suspected myocarditis following COVID-19 vaccination may be warranted to determine the frequency and evolution of this finding.

Risk factors and mechanisms for the development of suspected myocarditis following COVID-19 vaccination are unknown. White, non-Hispanic Americans comprised nearly 60% of those who had at least 1 vaccine dose in the United States prior to July 4, 2021.[26] Thus, race/ethnic distributions observed in our study likely reflect differences in vaccination rates rather than susceptibility. Males outnumber females in non-vaccine forms of myocarditis in both childhood[27] and adulthood,[28, 29] particularly with pseudo-infarct presentation, with the highest incidence in adolescent and young adult males.[29] Although 66-77% of non-COVID-19 myocarditis occurs in males,[27, 29] the male predominance in suspected VAM is strikingly higher, with males constituting 90.6% of cases in our series and all cases in smaller earlier reports.[6-8, 19] The underlying genetic differences or immune response mechanisms that underly the profound susceptibility of young males in VAM are uncertain. Mechanisms of myocardial dysfunction posited in MIS-C, such as hyperinflammatory state and cytokine storm[30] autoantibodies,[31, 32] or molecular

mimicry,[33] may play a role. Other potential mechanisms including reaction to adjuvant, nanoparticles, or other components of the vaccine[34] could also be important mechanistically. Negron *et al* have suggested an abundance of the SARS-CoV-2 Spike protein S1 subunit, produced as a result of mRNA vaccines, could interact with toll-like receptor 4, activate NF-kB, thereby eliciting cardiac inflammation and myocyte toxicity.[35] Further studies are critically needed to elucidate risk factors and underlying mechanisms for the development of potential VAM.

Optimal treatment strategies for clinically suspected VAM are unknown, with treatments ranging in our series from no anti-inflammatory therapies to glucocorticoids with or without IVIG, and even anakinra in one case. Glucocorticoids have not been shown to be beneficial, and may be harmful, in viral myocarditis. However, they have been used in virus-negative myocarditis.[12, 13, 36, 37] Clinicians may have administered immunomodulatory agents to some patients in this series because VAM results from an immune-mediated response, rather than direct viral infection of the myocardium.[34] The use of IVIG and glucocorticoids in ~20% of patients in this series may also reflect extrapolation from care strategies of MIS-C and non-COVID-19 myocarditis. Glucocorticoids and IVIG, alone or in combination, are used commonly in MIS-C,[38] with studies suggesting recovery of cardiac function[39] and decreased risk of development of left ventricular dysfunction and shorter ICU stays[40] when used in combination. Despite equivocal data[41, 42] and some recommendations against its use in non-COVID-19 myocarditis,[13, 42] NSAIDs were the most commonly used medication in our series. However, we could not discern whether NSAIDs were prescribed for pain management, for anti-inflammatory effects, or for both. Similarly, though colchicine is used in the treatment of pericardial disease,[43] it is not indicated for the treatment of myocarditis. Its use in nearly 8% of patients in this series may reflect concerns for pericardial involvement, *i.e.*, myopericarditis. Finally, we did not have sufficient sample size to analyze the efficacy of different medical regimens with propensity-score matching.

While VAM, even if mild in the majority, is a cause of great concern, its risk must be balanced against critical illness and cardiovascular involvement associated with acute or post-acute sequelae of COVID-19 infection,[44] and particularly with MIS-C in youth.[44-46] In large studies of MIS-C patients,

73.8% have been admitted to the ICU,[44] 30-62% have required inotropic/vasoactive support, [44-46] 3.3% were on ECMO and 1.9% died.[44] Children and adolescents with acute COVID-19 can also be quite ill; Feldstein *et al.* reported that 43.8% of hospitalized patients <21 years old with acute COVID-19 were admitted to an ICU, of whom 8.7% were on vasoactive support, 1.4% on ECMO, and 1.4% died.[44] Cardiovascular injury or involvement is common in MIS-C, with decreased LVEF in 34.2-52.0%[44-46] and coronary artery aneurysms in 13.4%.[44] In contrast to MIS-C and hospitalized pediatric COVID-19 patients, the frequencies of ICU admission and of inotropic/vasoactive support were only 18.7% and 1.4%, respectively, in our suspected VAM series. Frequency of left ventricular systolic dysfunction was lower (18.7%) than that reported in MIS-C. Some studies have suggested that diastolic dysfunction parameters persist, despite normalization of systolic function in COVID-19 suspected myocarditis.[47, 48] However, diastolic function and strain parameters were not assessed in our case series, so direct comparisons could not be performed.

The definition of myocarditis varies somewhat in the literature. Endomyocardial biopsy is the current reference standard to confirm the diagnosis of myocarditis,[12, 13, 49] but it is used infrequently in pediatrics[49] and adults.[12] Furthermore, a high false-negative rate has been reported in myocarditis, because biopsy samples are taken randomly and myocarditis tends to be focal.[49] In the 2021 American Heart Association Diagnosis and Management of Myocarditis in Children Statement, a "paradigm shift" in the diagnosis of myocarditis is described, with greater reliance on tissue characterization via cMRI.[49] None of the patients in our series underwent myocardial biopsy to confirm the diagnosis of myocarditis, likely reflecting clinical practice and an unfavorable risk/benefit ratio in children and young adults who recovered quickly following presentation with suspected myocarditis.

While this case series cannot determine causality of suspected myocarditis from COVID-19 vaccination, the number of cases of suspected myocarditis within a short-time frame after COVID-19 vaccination would be unlikely to be secondary to chance alone. The CDC has determined that the observed frequency of reporting of suspected myocarditis/pericarditis temporally related to COVID-19 vaccination is higher than the expected background rate of myocarditis/pericarditis.[50]

Our study design did not allow us to estimate the incidence or risk of myocarditis in adolescents and young adults after COVID-19 vaccine or to compare these risks with those from severe cardiac effects in youth following acute COVID-19 or MIS-C within each center's catchment area. Of note, the CDC has estimated reporting rates of 62.75 (0.006%) and 50.2 (0.005%) myocarditis cases per 1 million mRNA COVID-19 vaccine doses administered in the 12-17 and 18-24 year-old age groups, respectively.[22] Using data from Washington state, Schauer *et al*. estimated an incidence of 0.008% in adolescents aged 16-17 years and 0.01% in those aged 12-15 years.[20] The benefit-risk analysis presented by the CDC has suggested a positive balance for all age groups of both sexes, though the balance varies by age and sex; assessments of benefit-risk for each individual are also necessary.[11, 22]

Other limitations to this study relate to its retrospective and descriptive nature. The evaluation for alternative etiologies and management strategies for suspected myocarditis, such as indications for ICU admission, were decided by local clinicians rather than by study protocol. Furthermore, no patients underwent endomyocardial biopsy to rule out direct viral infection of myocardium. Therefore, some patients included in this series may have an alternative diagnosis, though the high numbers of clinically suspected myocarditis presenting within a week of vaccination in a 3-month period would be unusual. Also, approaches to image acquisition of cardiac MRIs were not standardized and relied on local protocols. Similarly, echocardiograms and cMRIs were not interpreted in core laboratories, and we did not assess diastolic function parameters. As cMRIs were obtained in only 69.3% of cases in our series at the time of submission, we may be over- or underestimating the frequency of abnormal cMRI findings. There may also be selection bias in who underwent cMRIs, though in our analysis, there was no statistical difference in troponin levels, frequency of LVEF<55%, or ICU stays between those who underwent cMRIs vs. those who did not. The variable timing at which cMRIs were obtained may also make findings (or lack of) findings difficult to interpret. We only studied the acute course of patients and do not have appreciable follow-up information. Patients in this series were evaluated at academic medical centers and may have been more seriously ill than cases in the community.

In conclusion, our case series demonstrates that myocarditis temporally related to COVID-19 vaccination is characterized by a mild illness with rapid resolution of symptoms in most patients. However, longer-term outcome data are lacking. We emphasize the importance of reporting suspected myocarditis cases after COVID-19 vaccination to the US Vaccine Adverse Events Reporting System or similar reporting systems for patients in other countries to better define the characteristics of this syndrome and its relationship to receipt of COVID-19 vaccines. Future studies that focus on determining risk factors and mechanisms of development of myocarditis are urgently needed, particularly as COVID-19 vaccines become more widely available to younger children in the future.

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Supplemental Materials

Supplemental Table 1: Evaluation for Alternative Microbial Etiologies of Myocarditis

Supplemental Table 2: Cardiac Magnetic Resonance Imaging Data by Site

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Table 1. Centers for Disease Control and Prevention Case Definitions for Probable and Confirmed Cases of COVID-19 Vaccine Associated Myocarditis[11]

Probable Case	Confirmed Case
• ≥1 new or worsening symptom: o Chest pain, pressure or discomfort o Dyspnea or shortness of breath o Palpitations o Syncope • AND ≥ 1 new finding of: o Elevated troponin o Abnormal ECG or rhythm monitoring consistent with myocarditis o Abnormal ventricular systolic function or wall motion abnormality on echocardiogram o cMRI findings consistent with the original or revised Lake Louise criteria for myocarditis[14] • AND no other identifiable cause of the symptoms and findings	• ≥1 new or worsening symptom: o Chest pain, pressure or discomfort o Dyspnea or shortness of breath o Palpitations o Syncope • AND o Histologic confirmation of myocarditis OR o Elevated troponin AND cMRI findings consistent with the original or revised Lake Louise criteria for myocarditis[14] • AND no other identifiable cause of the symptoms and findings

ECG=electrocardiogram; cMRI=cardiac magnetic resonance imaging

Table 2. Demographic Variables and History of COVID-19 Infection	
	N=139
Age (years)	15.8 (range 12.1-20.3; IQR 14.5-17.0)
12 to <16 years old	73 (52.5%)
16 to ≤20 years old	66 (47.5%)
Sex (male)	126 (90.6%)
Race	
White	92 (66.2%)
Black	6 (4.3%)
Asian	9 (6.5%)
Native American/Alaskan native	2 (1.4%)
Other	13 (9.4%)
Unknown/Refused to answer	17 (12.2%)
Ethnicity	
Hispanic	29 (20.9%)
Unknown/Refused to answer	14 (10.1%)
Known prior COVID-19 infection	
Yes (by history)	10 (7.2%)
Months from known COVID-19 infection	5 (range <1-10)
Yes (by COVID-19 nucleocapsid antibody) (N=82)	10 (7.2%)
No history and/or negative nucleocapsid antibody	94 (67.6%)
Unknown history and no nucleocapsid antibody tested	30 (21.6%)

Table 3. COVID-19 Vaccine and Clinical Data	
	N=139
Brand of COVID-19 vaccine	
Pfizer-BioNTech	131 (94.2%)
Moderna	5 (3.6%)
Johnson and Johnson	1 (0.7%)
Unknown	2 (1.4%)
Dose of Vaccine with Symptoms (N=140)	
1st dose	12 (8.6%)
2nd dose	128 (91.4%)
Days from vaccine administration to symptom onset	2 (range 0-22; IQR 1-3)
Symptoms	
Chest pain	138 (99.3%)
Fever (temperature ≥100.4F or tactile)	43 (30.9%)
Shortness of breath	38 (27.3%)
Headache	22 (15.8%)
Myalgias	19 (13.7%)
Vomiting	17 (12.2%)
Fatigue	11 (7.9%)
Palpitations	7 (5.0%)
Rash	5 (3.6%)
Diarrhea	3 (2.2%)
Conjunctivitis	1 (0.7%)
Intensive care unit stay	26 (18.7%)
Inotropes used	2 (1.4%)
Hospital length of stay (days)	2 (range 0-10; IQR 2-3)
Mortality	0

Table 4. Laboratory, ECG, and Imaging Data	
Peak lab values	
Troponin (N=139)	
Troponin I (ng/mL) (N=111) (Reference normal <0.04 ng/mL)	8.12 (IQR 3.50-15.90)
Troponin T (ng/mL) (N=28) (Reference normal ≤0.014 ng/mL)	0.61 (IQR 0.25-1.30)
BNP (pg/mL) (N=101) (Reference normal <100 pg/mL)	55.0 (IQR 18.9-147.0)
NT-Pro-BNP (pg/mL) (N=8) (Reference normal <125 pg/mL)	159 (IQR 91.5-810.3)
C-Reactive protein (mg/dL) (N=116) (Reference normal <0.3 mg/dL)	3.3 (IQR 1.1-6.2)
Testing/Imaging	
ECG (N=138) Abnormal Normal	 97 (69.8%) 41 (29.5%)
Abnormal ECG findings or arrhythmias (N=97)	
ST or T wave changes/elevation	95 (97.9%)
Non-sustained VT (ECG, telemetry, or ambulatory monitoring)	7 (5.0%)
Low voltage QRS	5 (3.6%)
PVCs (ECG, telemetry, or ambulatory monitoring)	3 (2.2%)
Atrial tachycardia (ECG, telemetry, or ambulatory monitoring)	1 (0.7%)
Premature atrial contractions	1 (0.7%)
First degree atrioventricular block	1 (0.7%)
Complete heart block	1 (0.7%)
Echocardiogram (N=139) Left ventricular ejection fraction	
Normal/≥55%	113 (81.3%)
Mild dysfunction (45-54%)	22 (15.8%)
Moderate dysfunction (35-44%)	2 (1.4%)
Severe dysfunction (<35%)	2 (1.4%)
Pericardial effusion ≥small in size	1 (0.7%)
Cardiac MRI (N=97)	
Days from symptom onset to cardiac MRI	5 (range 1-88; IQR 3-17)
Left ventricular ejection fraction	60.0% (55.0-62.7%)
Right ventricular ejection fraction	57.3% (52.9-62.0%)
Abnormal findings	75 (77.3%)
Late gadolinium enhancement	74 (98.7%)
Myocardial edema	54 (72.0%)
Lake Louise criteria (Yes)	49 (50.5%)
CDC case definition of myocarditis (N=140)	
Confirmed	49 (35.0%)
Probable	91 (65.0%)

BNP=Brain natriuretic peptide; ECG=electrocardiogram; PVC=Premature ventricular contraction; MRI=magnetic resonance imaging; CDC=Centers for Disease Control and Prevention

Figure Legends

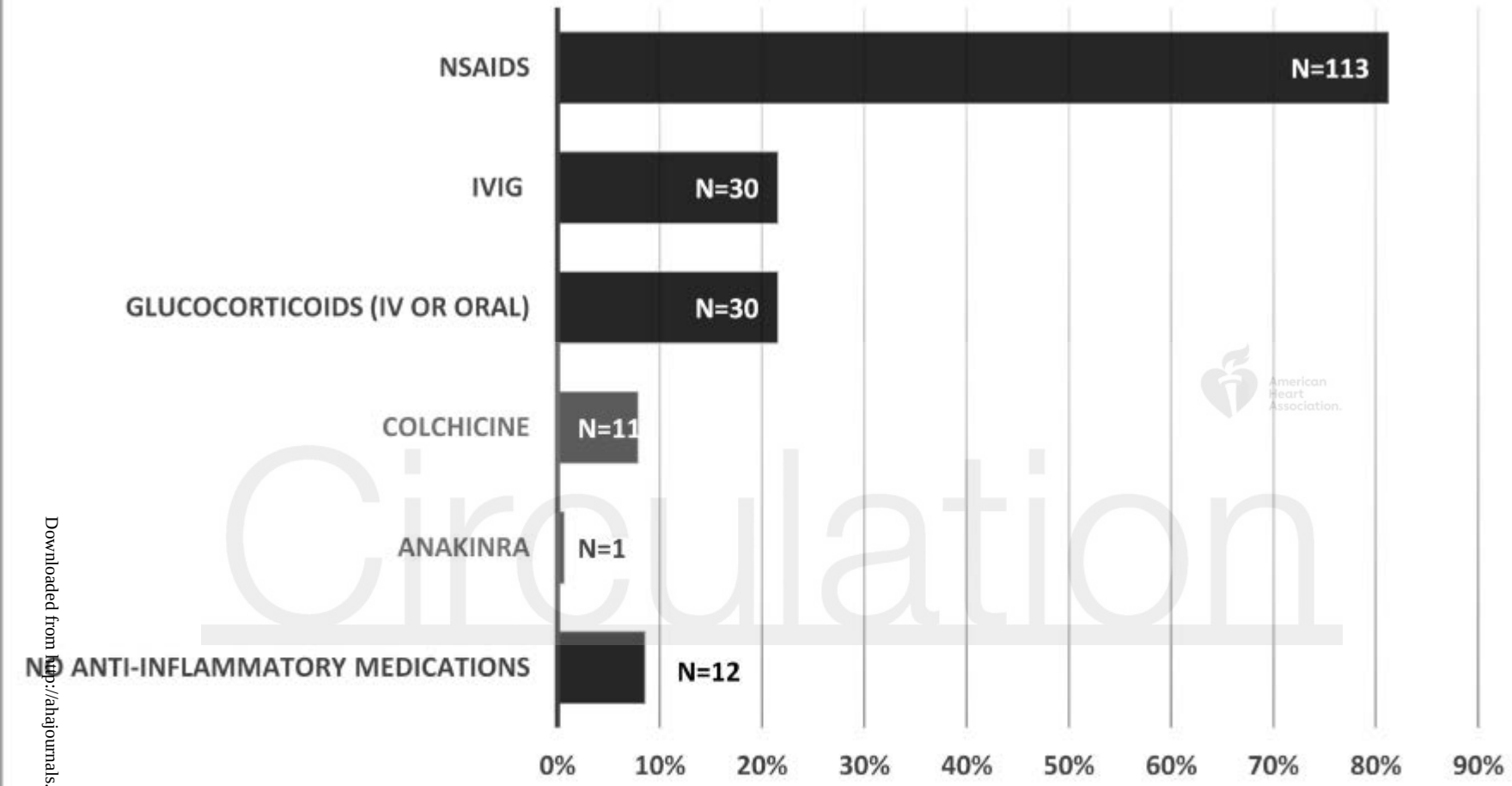
Figure 1. Anti-inflammatory therapies used in the treatment of suspected myocarditis temporally related to COVID-19 vaccination.

Figure 2. Electrocardiographic abnormalities and rhythm disturbances seen in suspected myocarditis temporally related to vaccination.

(a) Diffuse ST elevation on the electrocardiogram of a 15-year-old male presenting with chest pain and elevated troponin levels 2 days after his 2nd Pfizer vaccine dose. (b) Holter monitor tracing showing a 15 beat run of non-sustained ventricular tachycardia at a rate of ~170 beats per minute in a 17-year-old male who had ventricular couplets and a 3 beat run of non-sustained ventricular tachycardia during hospitalization for suspected myocarditis following his 2nd Pfizer-BioNTech vaccine dose.

Figure 3.

Cardiac magnetic resonance images from a 16-year-old male (a,c) obtained 5 days after 2nd dose (2 days after symptom onset) and a 15-year-old male (b,d) 4 days after 2nd dose (2 days after symptom onset). T2 weighted images (a, c) show focal inferolateral wall edema. Late gadolinium enhancement images (b,d) show subepicardial and mid-wall enhancement characteristic of myocarditis.



NSAIDs=Nonsteroidal anti-inflammatory drugs; IVIG=Intravenous immunoglobulin