

Multisystem Inflammatory Syndrome in Adults After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection and Coronavirus Disease 2019 (COVID-19) Vaccination

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Background. Multisystem inflammatory syndrome in adults (MIS-A) was reported in association with the coronavirus disease 2019 (COVID-19) pandemic. MIS-A was included in the list of adverse events to be monitored as part of the emergency use authorizations issued for COVID-19 vaccines.

Methods. Reports of MIS-A patients received by the Centers for Disease Control and Prevention (CDC) after COVID-19 vaccines became available were assessed. Data collected on the patients included clinical and demographic characteristics and their vaccine status. The Vaccine Adverse Events Reporting System (VAERS) was also reviewed for possible cases of MIS-A.

Results. From 14 December 2020 to 30 April 2021, 20 patients who met the case definition for MIS-A were reported to CDC. Their median age was 35 years (range, 21–66 years), and 13 (65%) were male. Overall, 16 (80%) patients had a preceding COVID-19-like illness a median of 26 days (range 11–78 days) before MIS-A onset. All 20 patients had laboratory evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Seven MIS-A patients (35%) received COVID-19 vaccine a median of 10 days (range, 6–45 days) before MIS-A onset; 3 patients received a second dose of COVID-19 vaccine 4, 17, and 22 days before MIS-A onset. Patients with MIS-A predominantly had gastrointestinal and cardiac manifestations and hypotension or shock.

Conclusions. Although 7 patients were reported to have received COVID-19 vaccine, all had evidence of prior SARS-CoV-2 infection. Given the widespread use of COVID-19 vaccines, the lack of reporting of MIS-A associated with vaccination alone, without evidence of underlying SARS-CoV-2 infection, is reassuring.

Keywords. coronavirus; COVID-19; MIS-A; MIS-C; multisystem inflammatory syndrome in adults.

A novel multisystem inflammatory syndrome in children (MIS-C) temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first described in April 2020, initially in the United Kingdom and subsequently in other countries [1–5]. Almost all patients reported in the United States had evidence of SARS-CoV-2 infection, with a delayed occurrence in most patients of 2–6 weeks after acute infection [5, 6]. A similar multisystem inflammatory syndrome was identified in adults (MIS-A) beginning in June 2020 [7]. The clinical course of both MIS-C and MIS-A predominantly includes fever, elevated inflammatory markers,

gastrointestinal symptoms such as vomiting and diarrhea, shock or hypotension, cardiac dysfunction, and in some cases rash and bilateral conjunctivitis [5, 7]. Similar to MIS-C, patients with MIS-A typically have evidence of prior SARS-CoV-2 infection by serologic testing [5, 7].

As the coronavirus disease 2019 (COVID-19) pandemic spread in multiple waves throughout the United States, the occurrence of MIS-C peaks followed COVID-19 peaks by 2–5 weeks [5]. As of June 2021, 4018 MIS-C cases have been reported to the Centers for Disease Control and Prevention's (CDC's) national surveillance system [8]. In contrast, during the same period, fewer than 150 MIS-A cases have been reported to CDC or published in the scientific literature [7]. The temporal association of both MIS-C and MIS-A with the COVID-19 pandemic, their delayed occurrence by 2–6 weeks after acute SARS-CoV-2 infection, evidence of generalized inflammation, and multi-organ involvement suggest that both syndromes result from a dysregulated immune response

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to SARS-CoV-2 infection [9, 10]. However, the mechanisms driving this immune dysregulation and any potential predisposing environmental or host factors are unknown.

Data on patients with MIS-A published in the scientific literature and spontaneously reported to CDC by health departments and clinicians across the United States were previously analyzed to learn more about the clinical phenotype of the illness [7]. Due to the theoretical risk of MIS-A after exposure to any SARS-CoV-2-derived antigen, MIS-A was included in the list of potential adverse events following COVID-19 vaccination to be monitored as part of the Food and Drug Administration (FDA) emergency use authorization (EUA) [11]. In the present analysis, we assessed the clinical characteristics of MIS-A patients reported to CDC after COVID-19 vaccines were authorized for use among adults in the United States and we compared the demographic and clinical features of patients with and without a vaccination history. For patients who received a COVID-19 vaccine, we evaluated timing of vaccine receipt in relation to the onset of MIS-A and presence or absence of evidence of natural SARS-CoV-2 infection.

METHODS

The analysis included clinical data from patients with suspected MIS-A identified from different sources, including spontaneous reporting by treating clinicians and state health departments, during the period 14 December 2020 to 30 April 2021. Clinical information was evaluated using the criteria in the CDC case definition for MIS-A (Table 1) [12]. The case definition included hospitalized patients with fever, primary and secondary clinical criteria, and laboratory evidence of inflammation and SARS-CoV-2 infection. Only patients who met the

CDC case definition for MIS-A were included in the analysis. In addition to the clinical data, information about the COVID-19 vaccine type, timing, and the number of doses administered was reviewed. Available laboratory evidence of natural SARS-CoV-2 infection by molecular testing and serology for anti-nucleocapsid antibody, which is not induced by spike-based vaccines, was also evaluated. All COVID-19 vaccines currently available in the United States are based on SARS-CoV-2 spike protein. Some cases following COVID-19 vaccine were reviewed by infectious disease specialists and other medical experts in CDC's Clinical Immunization Safety Assessment Project which is established to review adverse events for vaccines used in the United States [13]. Information from MIS-A patients was obtained using a case report form developed to collect demographic, clinical, laboratory, imaging and treatment data or by using information from the Vaccine Adverse Event Reporting System (VAERS) and available medical records. VAERS is the national passive surveillance system for adverse events after immunization, which is jointly operated by CDC and FDA [14].

Cases of MIS-A among vaccine recipients are required to be reported to VAERS as part of the COVID-19 vaccine EUAs [11]. A VAERS search was completed for reports received from 14 December 2020 to 30 April 2021, using text and automated coding searches for key terms from the MIS-A case definition. Cases were identified if one of the following three search strategies were fulfilled: (1) search for "systemic inflammatory response syndrome" which is the designated term by medical dictionary for regulatory activities (MedDRA) for the suspected diagnosis of multisystem inflammatory syndrome in adults; (2) text string search of "multi-system inflammatory syndrome," "MIS-A," "MISA," or "MIS-C" found in symptoms text, laboratory data, illness at time of vaccination, preexisting illness, and

Table 1. Case Definition for Multisystem Inflammatory Syndrome in Adults

A patient aged ≥ 21 years hospitalized for ≥ 24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (eg, bacterial sepsis, exacerbation of chronic medical condition).

I. Clinical criteria

Subjective fever or documented fever (≥ 38.0 C) for ≥ 24 hours prior to hospitalization or within the first 3 days of hospitalization^a and at least 3 of the following clinical criteria occurring prior to hospitalization or within the first 3 days of hospitalization.^a At least 1 must be a primary clinical criterion.

A. Primary clinical criteria

1. Severe cardiac illness

Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF $< 50\%$), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)

2. Rash AND nonpurulent conjunctivitis

B. Secondary clinical criteria

1. New-onset neurologic signs and symptoms

Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)

2. Shock or hypotension not attributable to medical therapy (eg, sedation, renal replacement therapy)

3. Abdominal pain, vomiting, or diarrhea

4. Thrombocytopenia (platelet count $< 150\,000$ / microliter)

II. Laboratory evidence

The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.

A. Elevated levels of at least 2 of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin

B. A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection

Abbreviations: IL-6, interleukin 6; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aThese criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0. The case definition is available at <https://www.cdc.gov/mis-c/mis-a/hcp.html>.

allergies on the initial VAERS report form; or (3) combinations of the following preferred terms: (a) “pyrexia” and (b) “myocarditis,” or “conjunctivitis” or “rash”; and (c) “abdominal pain upper” or “thrombocytopenia” or “shock” or “encephalopathy”; and (d) “ESR increased” or “C-reactive protein increased” or “serum ferritin increased” or “procalcitonin increased.”

Demographic and clinical data of MIS-A patients who received the COVID-19 vaccine were compared with those of MIS-A patients who did not receive the vaccine. Fisher exact tests were used to assess differences in categorical variables, and Mann-Whitney *U* tests were used to assess differences in continuous variables. When available, the timing of preceding COVID-19 illness onset, SARS-CoV-2 laboratory testing, and/or COVID-19 vaccination dates were assessed and described in relation to MIS-A onset. The activity was determined to meet criteria for public health surveillance as defined in 45 CFR 46.102(l) [2] at the CDC.

RESULTS

From 14 December 2020 to 30 April 2021, 26 patients with suspected MIS-A were reported to CDC. Of these, 20 (77%) patients met the case definition for MIS-A and are included in the present analysis. The demographic and clinical characteristics of these MIS-A patients are summarized in Tables 2 and 3. The median age of the patients was 35 years (range, 21–66 years), and 13 (65%) patients were male (Table 2). Eight (40%) patients were non-Hispanic White, 7 (35%) were non-Hispanic Black, 2 (10%) were Hispanic, 2 (10%) were non-Hispanic Asian, and 1 (5%) was listed as multiple races. Overall, 16 (80%) of the 20 patients had a preceding COVID-19-like illness, 3 of the 4 patients without preceding COVID-19-like illness had a history of COVID-19 exposure, and previous exposure or illness status was unknown for 1 patient. All 20 patients had a positive viral or antibody test for SARS-CoV-2 confirming past or current infection: 15 (80%) patients tested positive by serology, 15 (80%) patients by reverse transcription polymerase chain reaction (RT-PCR), and 10 (50%) by both serology and RT-PCR. Previous COVID-19 illness was reported a median of 26 days (range 11–78 days) before MIS-A onset.

Seven MIS-A patients (35%) received COVID-19 vaccine before MIS-A onset. Demographic and clinical characteristics of these 7 patients were generally similar to the 13 MIS-A patients who had not received a COVID-19 vaccine (Table 2), although a greater proportion of the vaccinated MIS-A patients (71%) were female. All 7 were reported to CDC and were found on the retrospective VAERS search. No additional MIS-A patient was identified by VAERS search alone. Four patients received the Pfizer-BioNTech vaccine, and 3 patients received the Moderna vaccine. Six of the patients had a history of prior COVID-19 illness and 1 patient had a history of exposure to patients with COVID-19 before MIS-A onset. Six of the 7 patients tested

positive for SARS-CoV-2 by RT-PCR; the seventh patient that was negative by RT-PCR tested positive by anti-nucleocapsid serology (Table 3). Among the 7 patients who received a COVID-19 vaccine, the first dose was given a median of 10 days (range, 6–45 days) before MIS-A onset (Figure 1). Three of those 7 patients received the second dose of COVID-19 vaccine prior to MIS-A onset (4, 17, and 22 days before MIS-A onset). One patient received the second dose 18 days after MIS-A onset or 4 days after hospital discharge and had no reported complications following the second dose.

Almost all MIS-A patients developed gastrointestinal and cardiovascular manifestations. The predominant signs and symptoms included diarrhea (80%), abdominal pain (60%), vomiting (60%), rash (55%), headache (55%), and shortness of breath (45%) (Table 2). Cough and conjunctival injection were reported in less than one-third of patients. The most common clinical findings reported in at least half of the patients included hypotension (80%), shock (75%), cardiac dysfunction (75%), myocarditis (70%), and acute kidney injury (60%). Almost all patients (95%) were treated with corticosteroids, and 65% of patients received at least 1 dose of intravenous immunoglobulin (IVIG). Six (46%) of the 13 patients treated with IVIG were given a second dose. The median number of days of hospitalization among MIS-A patients was 6 days (range, 2–41 days); 14 (70%) of the patients were admitted to the intensive care unit (ICU). Overall, 2 (10%) of the MIS-A patients died, of whom 1 had received COVID-19 vaccine.

DISCUSSION

MIS-A is a rare, poorly understood complication of SARS-CoV-2 infection believed to result from a delayed dysregulated immune response to the virus [9, 10]. The patients summarized in the present article have evidence of hyperinflammation, including fever, elevated laboratory markers of inflammation, and multisystem organ involvement. Onset of MIS-A occurred a median of about 1 month after initial SARS-CoV-2 infection, consistent with findings from other reports describing patients with MIS-A and MIS-C [5, 7]. The clinical manifestations of MIS-A are generally similar to those of MIS-C with both involving fever, gastrointestinal and cardiovascular involvement, and elevated laboratory markers of inflammation [5, 7]. As described in Table 1, before diagnosing MIS-A other more likely alternative diagnosis such as bacterial sepsis should be excluded. Based on patients reported to CDC and published in the literature, MIS-A appears to occur much less frequently than MIS-C. As of May 2021, the total number of MIS-A patients reported to CDC and in the published literature are below 150, whereas over 3700 MIS-C cases have been reported to CDC as of the same month [7, 8]. Patients with MIS-A reported to date typically have a more severe illness course with higher rates

Table 2. Characteristics of Patients With Multisystem Inflammatory Syndrome in Adults by COVID-19 Vaccination Status, December 2020 to April 2021, United States

	Total (n = 20)	Vaccinated (n = 7)	Unvaccinated (n = 13)	P-value
Age in years, median (range)	35 (21–66)	37 (22–49)	35 (21–66)	.843
Sex				.022
Female	7 (35%)	5 (71%)	2 (15%)	
Male	13 (65%)	2 (29%)	11 (85%)	
Race/Ethnicity				
Non-Hispanic Asian	2 (10%)	0 (0%)	2 (15%)	.521
Hispanic	2 (10%)	0 (0%)	2 (15%)	.521
Multiple	1 (5%)	1 (14%)	0 (0%)	.350
Non-Hispanic Black	7 (35%)	2 (29%)	5 (38%)	1.000
Non-Hispanic White	8 (40%)	4 (57%)	4 (31%)	.356
Signs and symptoms				
Diarrhea	16 (80%)	7 (100%)	9 (69%)	.249
Abdominal pain	12 (60%)	6 (86%)	6 (46%)	.158
Vomiting	12 (60%)	3 (43%)	9 (69%)	.356
Rash	11 (55%)	3 (43%)	8 (62%)	.642
Headache	11 (55%)	3 (43%)	8 (62%)	.642
Shortness of breath	9 (45%)	5 (71%)	4 (31%)	.160
Chest pain or tightness	7 (35%)	2 (29%)	5 (38%)	1.000
Cough	6 (30%)	4 (57%)	2 (15%)	.122
Conjunctival injection	5 (25%)	2 (29%)	3 (23%)	1.000
Clinical findings				
Hypotension	16 (80%)	6 (86%)	10 (77%)	1.000
Shock	15 (75%)	6 (86%)	9 (69%)	.613
Cardiac dysfunction	15 (75%)	6 (86%)	9 (69%)	.613
Myocarditis	14 (70%)	4 (57%)	10 (77%)	.613
Acute kidney injury	12 (60%)	4 (57%)	8 (62%)	1.000
Pleural effusion	10 (50%)	4 (57%)	6 (46%)	.350
Pericardial effusion	9 (45%)	5 (71%)	4 (31%)	.160
Pneumonia	8 (40%)	3 (43%)	5 (38%)	1.000
Mitral regurgitation	7 (35%)	2 (29%)	5 (38%)	1.000
ARDS	2 (10%)	0 (0%)	2 (15%)	.521
Coronary artery dilatation or aneurysm	1 (5%)	0 (0%)	1 (8%)	1.000
Laboratory tests				
Elevated troponin	17 (85%)	6 (86%)	11 (85%)	1.000
Elevated BNP or NT-proBNP	16 (80%)	6 (86%)	10 (77%)	1.000
Thrombocytopenia	9 (45%)	4 (57%)	7 (54%)	.642
Lymphopenia	13 (65%)	4 (57%)	9 (69%)	.651
Treatment				
Steroids	19 (95%)	7 (100%)	12 (92%)	1.000
Respiratory support, any	14 (70%)	6 (86%)	8 (62%)	.354
IVIg	13 (65%)	6 (86%)	7 (54%)	.329
Anticoagulation medication	13 (65%)	2 (29%)	11 (85%)	.022
Vasoactive medications	12 (60%)	4 (57%)	8 (62%)	1.000
Antiplatelet medication	9 (45%)	3 (43%)	6 (46%)	1.000
Intubation and mechanical ventilation	6 (30%)	2 (29%)	4 (31%)	1.000
Immune modulators ^a	4 (20%)	2 (29%)	2 (15%)	.587
Outcome				
Days in hospital, median (range)	6 (2–41)	6 (3–10)	6 (2–41)	.685
ICU admission	14 (70%)	5 (71%)	9 (69%)	1.000
Died	2 (10%)	1 (14%)	1 (8%)	1.000
SARS-CoV-2 testing				
Any positive laboratory test	20 (100%)	7 (100%)	13 (100%)	1.000
PCR positive/Serology negative, not done, or missing	5 (25%)	2 (29%)	3 (23%)	1.000
Serology positive/PCR negative	5 (25%)	1 (14%)	4 (31%)	.613
PCR positive/Serology positive	10 (50%)	4 (57%)	6 (46%)	1.000

Table 2. Continued

	Total (n = 20)	Vaccinated (n = 7)	Unvaccinated (n = 13)	P-value
Vaccine doses				
0 dose	13 (65%)	0 (0%)	13 (100%)	...
1 dose	3 (15%)	3 (43%)	0 (0%)	...
2 doses ^b	4 (20%)	4 (57%)	0 (0%)	...
Preceding COVID-like illness	16 (80%)	6 (86%)	10 (77%)	1.000
Days from COVID-19 onset to MIS-A onset, median (range)	26 (11–78)	28 (25–43)	26 (11–78)	.913
Days from vaccination (1st dose) to MIS-A onset, median (range)	10 (6–45)	10 (6–45)	-	...

Abbreviations: ARDS, acute respiratory distress syndrome; BNP, B-natriuretic peptide; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MIS-A, multisystem inflammatory syndrome in adults; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aImmunomodulators were used in 4 patients: 3 received Anakinra and the 4th patient received tocilizumab.

^bThe 2nd dose in 1 patient was administered after recovery from MIS-A illness (Figure 1).

of shock and cardiac involvement. Compared to patients with MIS-C from previously published surveillance data, a higher proportion of the patients with MIS-A in the present analysis had shock (75% vs. 37%), cardiac dysfunction (75% vs 31%), myocarditis (70% vs 17%), and pericardial effusion (45% vs 23%) [5]. The higher rate of cardiac complications in MIS-A may be due to increased recognition, diagnosis, and reporting of patients with a more severe illness course.

Seven of the MIS-A patients in the present report received COVID-19 vaccine within 45 days (median 10 days) before MIS-A onset. However, all 7 patients also had evidence of prior SARS-CoV-2 infection. To date, no patient with MIS-A following COVID-19 vaccination without evidence of prior SARS-CoV-2 infection has been reported to CDC. Nune et al reported a 44-year-old woman who was hospitalized in the United Kingdom 2 days after receiving her first COVID-19 vaccination with arm pain, which progressed to fever, diarrhea, abdominal pain, rash, and hypotension [15]. The patient was reported to have tested negative for SARS-CoV-2 by serology and nasopharyngeal swabs. Two other publications reported similar patients who developed multisystem inflammatory syndrome after prior SARS-CoV-2 infection and receiving COVID-19 vaccine. Uwaydah et al reported a 22-year-old man from United Arab Emirates who was diagnosed with MIS-A 6 weeks after a mild COVID-19 illness [16]. The patient received the first dose of an inactivated SARS-CoV-2 vaccine about 30 days and second dose within hours before symptom onset of an illness that led him to visit the emergency department 4 days after vaccination; he was later diagnosed with MIS-A. Salzman et al reported 3 patients in the United States who were diagnosed with multisystem inflammatory syndrome after receiving COVID-19 vaccine [17]. These patients had illness onset within 20 days of receiving COVID-19 vaccine; 2 of the patients had acute COVID-19 about 6 weeks prior to illness onset and all three patients were positive by serology for nucleocapsid antigen. Reports of MIS-A following COVID-19 vaccination should be interpreted in the context of the large number of vaccinations administered in the

United States. Through 30 April 2021, 256 759 689 COVID-19 vaccine doses were administered to persons aged ≥21 years in the United States, including 111 842 926 doses of Moderna and 135 421 590 doses of Pfizer messenger RNA (mRNA) COVID-19 vaccines [18]. Given the widespread use of COVID-19 vaccines in the United States, the lack of reporting of MIS-A associated with vaccination alone, without evidence of underlying SARS-CoV-2 infection, is reassuring.

Although patients with MIS-A commonly reported prior COVID-19 illness, in some patients the only evidence of SARS-CoV-2 infection was a positive serology. All current COVID-19 vaccines elicit an immune response to the spike protein, and vaccinated patients are expected to be seropositive for anti-spike protein antibodies but not for anti-nucleocapsid antibodies. In contrast, natural infection with SARS-CoV-2 results in humoral responses to both the spike and nucleocapsid proteins, providing a plausible laboratory method to distinguish the immune response to vaccination from that resulting from natural infection [19]. However, anti-nucleocapsid antibody is not uniformly detectable following COVID-19 illness, so its absence does not necessarily rule out natural infection with SARS-CoV-2. In particular, younger patients with mild illnesses during acute infection with SARS-CoV-2 may be less likely to mount a humoral immune response to nucleocapsid protein [19].

The present analysis has several limitations. The MIS-A patients were spontaneously reported by health departments, but comprehensive surveillance for MIS-A does not currently exist, leading to potential underreporting of patients with MIS-A. Because VAERS is a passive surveillance system, underreporting of patients with MIS-A among vaccine recipients is also likely. Underreporting may particularly be true for MIS-A patients who have milder illness. Complications such as myocarditis were diagnosed by clinicians managing the patients and the methods used in the diagnosis were not standardized. Absence of imaging details may have limited our assessment of some findings such as pneumonia diagnosed on computed tomography.

Table 3. Demographic and Clinical Descriptions of Patients with Multisystem Inflammatory Syndrome in Adults Who Received a COVID-19 Vaccine, December 2020 to April 2021, United States

Patient	Age Group (years), sex	Race, Ethnicity	Onset Year	Serology	PCR	Clinical Features/ Imaging/ Complications	Treatment
1	20–24, Female	White, non-Hispanic	2021	Nucleo-capsid positive	Positive	Shock, shortness of breath, abdominal pain, diarrhea, neck pain, myalgia, cervical lymphadenopathy > 1.5 cm Echocardiography: LV dysfunction, EF 48%, pericardial effusion, ECG (T wave inversion), congestive heart failure, myopericarditis	Corticosteroids, IVIG ×1
2	20–24, Female	White, non-Hispanic	2021	Nucleo-capsid positive	Positive	Shock, cough, shortness of breath, abdominal pain, diarrhea, elevated bilirubin/liver function tests Echocardiography: LV dysfunction, pericardial effusion Abdominal CT: mesenteric lymphadenopathy Chest CT: pneumonia, pleural effusion congestive heart failure, myocarditis	HFNC, vasoactive medication, corticosteroids, antiplatelet medication, IVIG ×2
3	30–34, Female	White, non-Hispanic	2020	Nucleo-capsid positive	Positive	Shock, cough, abdominal pain, vomiting, diarrhea, rash, myalgia, elevated LFTs Echocardiography: LV dysfunction, EF 44%, mild LV hypertrophy, mild pulmonary hypertension, mild pericardial effusion Chest CT/X-ray: pneumonia ECG (non-specific ST seg change, abnormal T-wave), congestive heart failure	HFNC, corticosteroids
4	35–39, Male	White, non-Hispanic	2021	Nucleo-capsid positive	Negative	Shock, abdominal pain, vomiting, diarrhea, rash, headache, myalgia, conjunctival injection, cervical lymphadenopathy, altered mental status Elevated bilirubin/liver function tests Echocardiography: LV/RV dysfunction, pericardial/pleural effusion, mitral regurgitation Chest X-ray: patchy airspace disease congestive heart failure, myocarditis, AKI	Mechanical ventilation, ECMO, vasoactive medication, corticosteroids, antiplatelet medication, IVIG ×2
5	45–49, Female	Multiple races, non-Hispanic	2021	Nucleo-capsid positive	Positive	Shortness of breath, diarrhea, rash, mucocutaneous lesions, encephalopathy, myalgia Elevated liver function tests Echocardiography: normal Chest CT: atelectasis Encephalitis or aseptic meningitis, AKI	Non-invasive ventilation, corticosteroids, antiplatelet medication, IVIG ×1
6	45–49, Male	Black, non-Hispanic	2021	Not done	Positive	Shock, cough, shortness of breath, chest pain, abdominal pain, diarrhea, headache, encephalopathy Elevated bilirubin/liver function tests, Echocardiography: cardiac dysfunction, reduced EF Abd CT: enlarged liver Chest CT: ground glass infiltrates, pneumonia, pleural effusion Arrhythmia (supraventricular), congestive heart failure, encephalitis or aseptic meningitis, AKI	Noninvasive ventilation, vasoactive medication, corticosteroids, tocilizumab, anticoagulation medication, IVIG ×1
7	45–49, Female	Black, non-Hispanic	2021	Nucleo-capsid positive	Positive	Shock, cough, chest pain, abdominal pain, vomiting, diarrhea, headache, syncope or near syncope, encephalopathy, cervical lymphadenopathy > 1.5 elevated bilirubin/liver function tests Echocardiography: LV/RV dysfunction, EF 25%, pericardial effusion, severe global LV hypokinesis Abdominal ultrasound: gallbladder thickening and trace pericholecystic fluid Chest X-ray: pleural effusion, opacity Congestive heart failure, myopericarditis, AKI, renal failure,	Mechanical ventilation, vasoactive medication, corticosteroids, anakinra, IVIG ×2

Abbreviations: AKI, acute kidney injury; CT, computed tomography; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; HFNC, high-flow nasal canula; IVIG, intravenous immune globulin; LFT, liver function test; LV, left ventricle; RV, right ventricle.

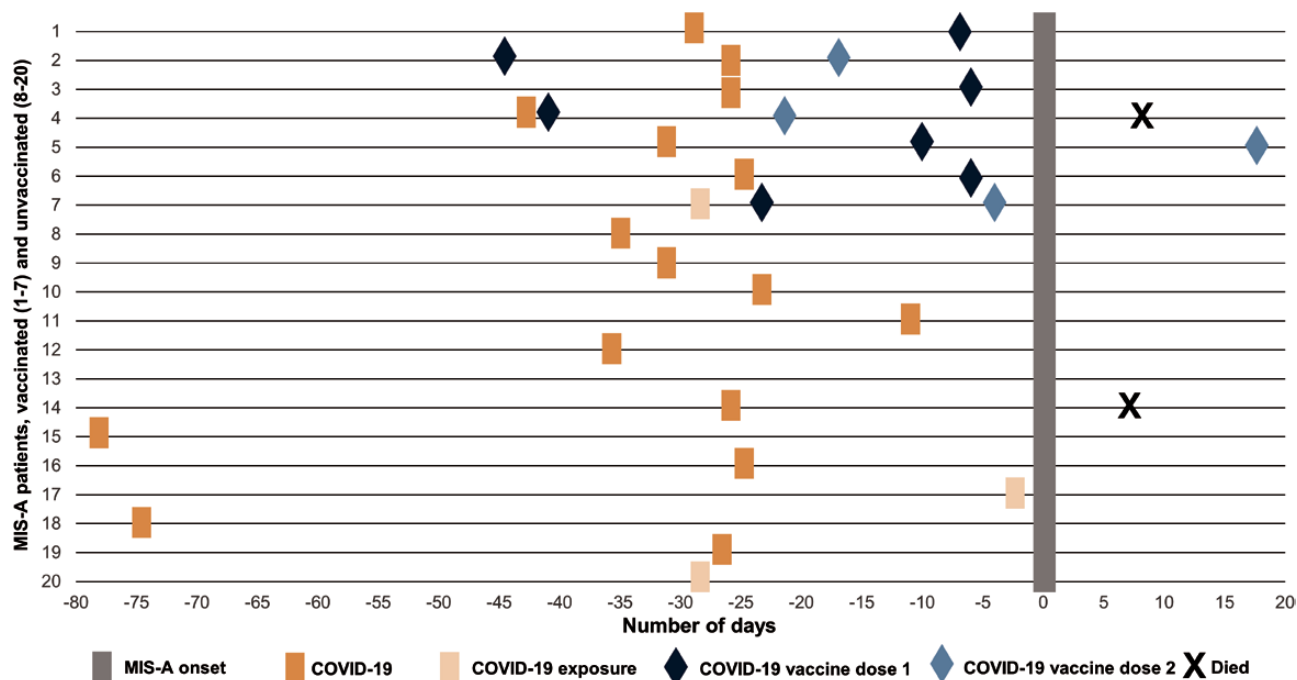


Figure 1. Patients with multisystem inflammatory syndrome in adults by illness onset and timing of prior COVID-19 illness and vaccine receipt. For patient 13, timing of previous COVID-19 illness or exposure was unknown. Abbreviations: COVID-19, coronavirus disease 2019; MIS-A, multisystem inflammatory syndrome in adults.

The treatment for MIS-A is generally adopted from treatment guidelines developed for MIS-C and primarily consists of administration of corticosteroid and IVIG either alone or in combination. These interventions, with possible addition of other adjunctive immunomodulatory treatment for patients not responding to IVIG and/or corticosteroids, were developed by expert opinion based on currently available evidence [20–22]. Additional treatment with vasopressors and antiplatelet and anticoagulation therapy may be required in some patients. Clinicians who identify patients with an illness similar to MIS-A in temporal association with the COVID-19 vaccine are encouraged to report such cases through VAERS; COVID-19 vaccine providers are required to report suspected MIS-A to VAERS as part of the EUAs. A case definition for MIS-A developed by CDC summarized in Table 1 can be used to assess patients suspected of having the illness [12].

CONCLUSION

MIS-A is a rare complication of SARS-CoV-2 infection. Patients developing MIS-A in temporal association with COVID-19 vaccination have been reported, although all patients reported to date also had evidence of prior SARS-CoV-2 infection. The potential contribution of vaccination to the pathogenesis of MIS-A in these patients is unclear. It is reassuring that, to date, no cases of MIS-A have been reported among vaccine recipients in the United States without evidence of prior SARS-CoV-2 infection despite the administration of COVID-19 vaccines to

millions of recipients. Clinicians should maintain a high index of suspicion for the occurrence of similar patients and report suspected cases of MIS-A and other serious adverse events following vaccination to VAERS.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC.

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