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# A Case of Adult Multisystem Inflammatory Syndrome Following COVID-19 Vaccine

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## Abstract

Multisystem inflammatory syndrome is a life-threatening condition associated with elevated inflammatory markers and multiple organ injury. A diagnosis of exclusion, it has been reported after severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2) in children and adults; recently it has been described in some post-COVID-19 vaccinated individuals. The prognosis with supportive care and immunomodulatory therapy is good, although some individuals may require treatment in the intensive care unit (ICU). Here we report a case of a 58-year-old man who developed multi-organ failure after receiving the second dose of the Moderna mRNA-1273 COVID-19 vaccine. He required critical organ support in the ICU. An extensive workup was done to rule out alternative infectious and inflammatory processes. Following a period of gradual in-hospital convalescence, our patient made a full recovery. To our knowledge, this is the first comprehensively described case of multisystem inflammatory syndrome associated with Moderna mRNA-1273 COVID-19 vaccine in an adult over 50 years of age.

**Keywords:** COVID-19 vaccine, Multisystem inflammatory syndrome in adults (MIS-A), Multisystem inflammatory syndrome in vaccinated individuals (MIS-V), Immunological products and vaccines, Intensive care, Vaccination/immunization, Acute tubular necrosis (ATN), Unwanted effects/Adverse reactions

## 1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) was first reported in England followed by other countries around the world.<sup>1</sup> It has been found to occur typically 4–6 weeks and up to 12 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, more commonly in healthy non-Hispanic black children,

with multiple organ involvement and has a favorable prognosis.<sup>1–3</sup> The syndrome is significant for involvement of the gastrointestinal tract (nausea, vomiting, diarrhea), cardiovascular system (circulatory shock, elevated troponin, myocarditis), renal system (AKI), mucocutaneous lesions, conjunctivitis, lymphadenopathy, alongside constitutional symptoms like fever and anorexia.<sup>1–3</sup> Patients have a hyperinflammatory milieu with some resemblance

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to Kawasaki disease, but the latter occurs predominantly in younger children (less than 3 years old). Treatment generally has been supportive care with immunomodulatory treatment consisting of corticosteroid and intravenous immunoglobulin (IVIG).<sup>1–3</sup>

Multisystem inflammatory syndrome in adults (MIS-A) has also been described, with a far lower incidence compared to MIS-C.<sup>1–3</sup> Compared to patients experiencing acute SARS-CoV-2 infection, these patients have a positive SARS-CoV-2 serology or recent infection and of note, absent or very minimal pulmonary symptoms.<sup>1,4,5</sup> Like MIS-C, adults experiencing this syndrome have a hyper-inflammatory milieu and multiple organ involvement, often needing critical care support along with immunomodulatory therapy. Antibody testing may establish the diagnosis if SARS-CoV-2 antigen or PCR testing is not available or negative.<sup>1,3,4</sup> In adults, the clinical presentation of MIS-A could be broad and therefore, it may be under-recognized and under-reported.<sup>4,5</sup> MIS following SARS-CoV-2 has demonstrated a consistently good response to steroids and/or IVIG.<sup>6,7</sup>

COVID-19 vaccinations play a crucial role in controlling the pandemic. As of February 14, 2022, more than 547 million doses of SARS-CoV-2 vaccine have been administered in the United States.<sup>8</sup> The validation and production of COVID-19 vaccines were expedited in response to the rapid spread of SARS-CoV-2. Most post-vaccination reactions occur within 3 days of receiving a dose and resolve within 1–2 days.<sup>7,9</sup> While MIS can usually be seen up to 12 weeks following SARS-CoV-2 infection, recently a handful of vaccine-associated cases have been reported in patients who likely had prior SARS-CoV-2 infection.<sup>3,6,7,10,11</sup> Vaccine-related MIS (MIS-V) has been reported in medical literature with both mRNA vaccine [Pfizer-Biontech, Moderna] and conventional inactivated vaccine [BBIBP-CorV (Sinopharm)] with good clinical description.<sup>3,6,7,11</sup> Although generally self-limiting, some individuals affected by MIS-V have required critical organ support in the intensive care unit (ICU). Here we report a case of a middle-aged individual who developed shock with multi-organ failure and persistent encephalopathy temporally associated with SARS-CoV-2 vaccination.

## 2. Case presentation

A 58-year Caucasian man with a past medical history of obesity (body mass index of 33), gastroesophageal reflux disease, and chronic back pain presented to the emergency department with a

### Abbreviations

|            |   |
|------------|---|
| Ab         | antibody  |
| AKI        | acute kidney injury   |
| ANCA       | antineutrophil cytoplasmic antibodies                         |
| ATN        | acute tubular necrosis  |
| CDC        | Centers for Disease Control and Prevention                    |
| COVID-19   | coronavirus disease 2019                                      |
| CSF        | cerebrospinal fluid   |
| CT         | computed tomography   |
| HHV        | human herpesvirus   |
| HIV        | human immunodeficiency virus                                  |
| HLH        | hemophagocytic lymphohistiocytosis                            |
| HSV        | herpes simplex virus  |
| ICU        | intensive care unit   |
| IVIG       | intravenous immunoglobulin                                    |
| MIS (A)    | multisystem inflammatory syndrome (in adults)                 |
| MIS (C)    | multisystem inflammatory syndrome (in children)               |
| MIS (V)    | multisystem inflammatory syndrome (in vaccinated individuals) |
| mRNA       | messenger ribonucleic acid                                    |
| NSAID      | non-steroidal anti-inflammatory drugs                         |
| PCR        | polymerase–chain reaction                                     |
| RV         | right ventricle   |
| SARS-CoV-2 | Severe acute Respiratory Syndrome Coronavirus-2               |

7-day history of headache, generalized weakness, nausea, and myalgias followed by a 1-day history of chills, profuse sweats, a fever in the range of 37.2–38.1 °C, and diarrhea. At presentation, he complained of progressive shortness of breath alongside vague abdominal pain and cramping, anorexia, and a rash on his lower extremities and back. He denied any prior dermatologic or rheumatologic conditions. He endorsed recent contact with livestock, domestic and wild animals, but denied any sick contacts or tick bites. Symptoms started one day after receiving the second dose of mRNA-1273 vaccine. He had received influenza, tetanus/diphtheria/pertussis, and hepatitis B vaccines in the past without adverse reactions and had no history of allergies. He denied any previous symptoms suggestive of SARS-CoV-2 infection, although a close contact did test positive for the same about 7 months prior to this presentation. He was a non-smoker, frequently consumed moderate amounts of alcohol, and regularly took acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). At the onset of symptoms, a polymerase–chain reaction (PCR) testing was negative for SARS-CoV-2.

On admission he was afebrile (35.5 °C), mildly tachypneic (22/min) with abdominal breathing, but normal oxygen saturation on room air, tachycardic



Fig. 1. Rash - Non specific blanching erythematous rash on the lower extremities sparing palms and soles.

(Heart rate:100/minutes), and normotensive (Blood pressure:110/70 mm Hg). There was presence of mild scleral icterus, and mild generalized

abdominal tenderness. An erythematous confluent blanching rash sparing his palms and soles was noted on his lower extremities and back (Fig. 1). His mucous membranes appeared normal. Although, physical examination and radiological studies demonstrated no evidence of pulmonary parenchymal disease, his declining respiratory status, increased work of breathing and progressive encephalopathy necessitated ICU admission, noninvasive ventilation, and subsequent intubation with mechanical ventilation. Upon arrival in the ICU, he was hypotensive and required ample fluid resuscitation (8 L) with dual vasopressor support, and broad-spectrum antibiotics were initiated. His shock was thought to be a combination of distributive and more likely cardiogenic shock.

Given his history and clinical presentation, the differential diagnosis was very broad and is listed in Table 1. Chest X-ray and computed tomography

Table 1. Differential diagnosis at presentation.

| Etiology                           | Condition   |
|------------------------------------|---|
| Infectious                         | <ul style="list-style-type: none"> <li>• Septic shock of unknown origin.</li> <li>• Toxic shock syndrome.</li> <li>• Staphylococcal and Streptococcal syndromes including Staphylococcal scalded skin syndrome, Scarlet fever.</li> <li>• Gastrointestinal tract infections such as Campylobacter, C. difficile toxin, Plesiomonas shigelloides, Salmonella species, Vibrio species, Vibrio cholerae, Yersinia species, Enteroaggregative E. coli (EAEC), Enteropathogenic E. coli (EPEC), Enterotoxigenic E. coli (ETEC), Shiga toxin producing E. coli, Shigella/Enteroinvasive E. coli, Cryptosporidium specie, Cyclospora cayetanensis, Entamoeba histolytica, Giardia, Astrovirus, Norovirus GI/GII, Rotavirus Ag, Sapovirus.</li> <li>• Tick-borne illnesses such as Lyme disease, Anaplasmosis, Babesiosis, Tularemia, Ehrlichiosis, and Rickettsia.</li> <li>• Bacterial/Viral meningoencephalitis including Adenovirus, Coronavirus, SARS Coronavirus-2, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial Virus, Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae, West Nile virus infection.</li> <li>• Diseases associated with animal exposure such as Leptospirosis, Bartonella, Brucella, Q fever, Francisella tularensis.</li> <li>• Viral diseases such as Epstein Barr virus, Enterovirus, Adenovirus, Parvovirus, Measles, Acute and Chronic viral hepatitis, Hanta virus.</li> <li>• Endemic fungi such as Histoplasma, Blastomyces.</li> <li>• HIV.</li> <li>• Malaria and Toxoplasmosis.</li> </ul> |
| Vasculitis                         | <ul style="list-style-type: none"> <li>• Cryoglobulinemia.</li> <li>• Rheumatoid arthritis.</li> <li>• Systemic Lupus erythematosus.</li> <li>• ANCA associated Vasculitis.</li> <li>• Goodpasture's syndrome</li> </ul>  |
| Miscellaneous                      | <ul style="list-style-type: none"> <li>• Drug reaction with eosinophilia and systemic symptoms (DRESS)</li> <li>• Macrophage activation syndrome</li> <li>• Hemophagocytic lymphohistiocytosis (HLH)</li> <li>• Multisystem Inflammatory Syndrome (MIS-A, MIS-V).</li> <li>• Vaccine-induced immune reaction</li> </ul>   |
| Causes of Acute Kidney injury(AKI) | <ul style="list-style-type: none"> <li>• Acute glomerulonephritis secondary to infectious/noninfectious etiology</li> <li>• Acute tubular necrosis/injury (ATN) secondary to Sepsis, hypotension and NSAIDs use.</li> <li>• Acute interstitial nephritis</li> <li>• Thrombotic microangiopathy</li> <li>• Non-monoclonal renal amyloid deposit</li> </ul>   |

(CT) angiogram of the chest ruled out pulmonary embolism and showed no evidence of acute pulmonary parenchymal disease. Abdominal CT showed nonspecific bilateral fascial thickening, mesenteric fat stranding and lymph node enlargement, mild splenomegaly along with some dilated small bowel loops suggestive of localized ileus. Electrocardiogram performed serially showed normal sinus rhythm with ST segment elevation in anterolateral leads (Fig. 2). Echocardiogram showed elevated right ventricular (RV) systolic pressure, moderately enlarged RV chamber size and hypokinesia; mildly increased concentric left ventricular wall thickness with grade 2/3 left ventricular diastolic dysfunction, and an ejection fraction of 45%. There was no pericardial effusion. Coronary angiogram showed no significant coronary artery stenosis. Magnetic resonance cholangiopancreatography ruled out any evidence of biliary obstruction.

Initial and subsequent abnormal laboratory results are enumerated in Table 2. There was a mild to moderate decrease in hemoglobin and platelet count without evidence of intravascular hemolysis or microangiopathic hemolytic anemia. An exhaustive infectious/auto immune/rheumatological disease work up including but not limited to GI pathogen panel, Respiratory viral panel, Tick borne panel, Rodent borne panel, Meningitis/encephalitis panel, work up for Facultative intracellular bacteria, intra erythrocytic parasites, Fungal infection panel, work up for diseases associated with animal exposure such as Leptospirosis, Bartonella, Brucella, Q fever, Francisella tularensis; Parasitic infection panel, Viral infection panel, Acute and Chronic hepatitis panel, HIV testing, auto immune and rheumatological panel, work up for atypical bacterial pneumonia, was found to be negative.

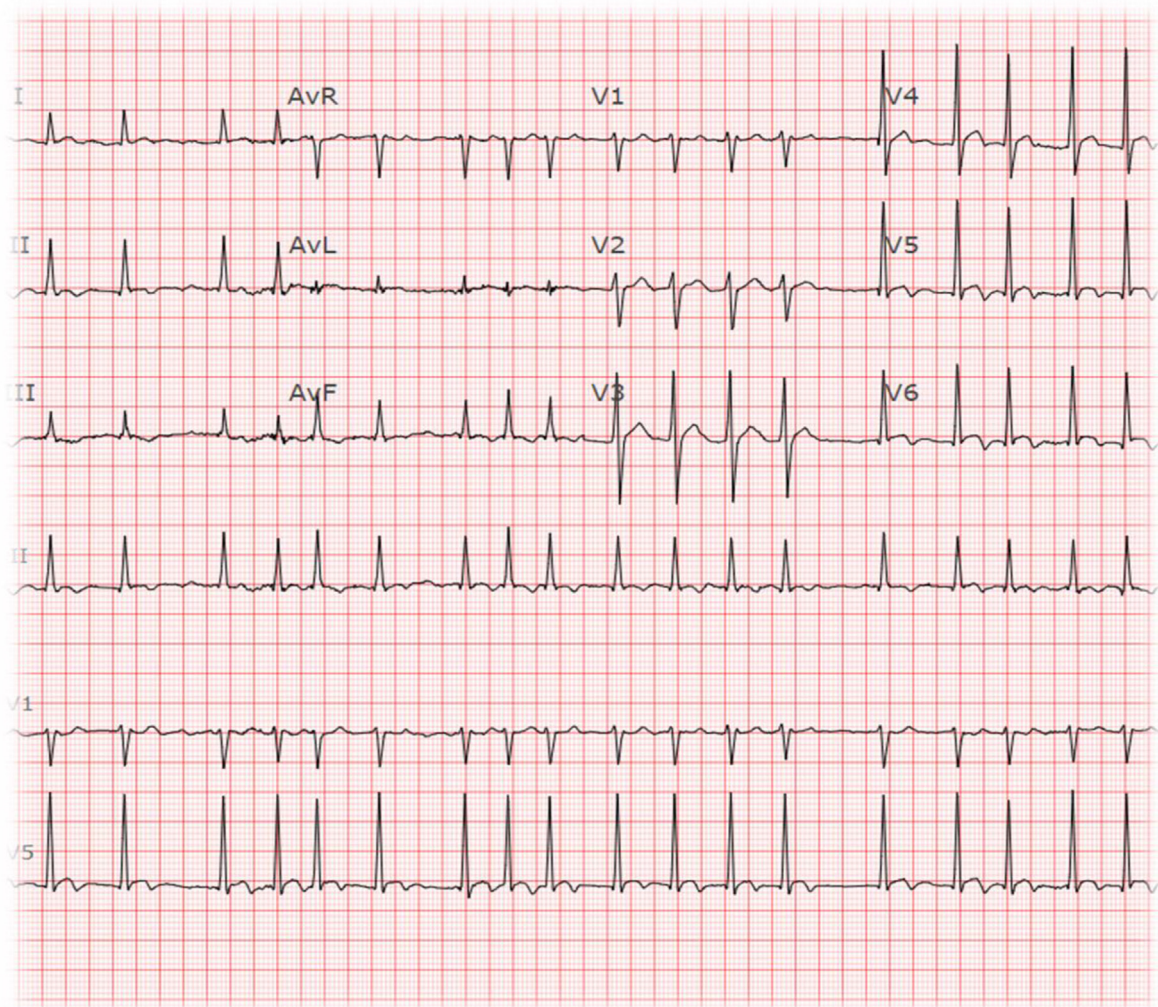


Fig. 2. Electrocardiogram on admission which showed nonspecific ST-T wave abnormality including some ST segment elevation and T wave inversion. In concert with elevated Troponin enzymes, there was concern for Myocarditis, pericarditis, and Non-ST elevation Myocardial Infarction.

Table 2. Abnormal initial and subsequent laboratory results.

|  | Result        | Normal range                  |
|--|---------------|-------------------------------|
| Laboratory results on admission:           |               |                               |
| Leucocytes                                 | 12,400 WBC/uL | 4.5–11.0 × 10 <sup>9</sup> /L |
| Thrombocytes                               | 132,000/uL    | 150–400 × 10 <sup>9</sup> /L  |
| Sodium                                     | 131 mmol/L    | 136–146 mmol/L                |
| Total bilirubin                            | 2.8 mg/dL     | 0.1–1.0 mg/dL                 |
| Direct bilirubin                           | 2.3 mg/dL     | 0.0–0.3 mg/dL                 |
| Alkaline phosphatase                       | 175 U/L       | 25–100 U/L                    |
| Troponin T enzyme baseline                 | 135 ng/L      | ≤15 ng/L                      |
| Troponin T enzyme at 2 h                   | 155 ng/L      | <10 ng/L                      |
| Troponin T enzyme at 6 h                   | 180 ng/L      | <12 ng/L                      |
| Laboratory results during hospitalization: |               |                               |
| C-reactive protein                         | 331 mg/L      | ≤8 mg/L                       |
| Triglycerides                              | 602 mg/dL     | <150 mg/dL                    |
| Ferritin                                   | 4236 mcg/L    | 20–250 µg/L                   |
| Lactate dehydrogenase                      | 248 U/L       | 45–200 U/L                    |
| Fibrinogen                                 | 780 mg/dL     | 200–393                       |
| Total bilirubin peak                       | 9.3 mg/dL     | <1.2 mg/dl                    |
| Direct bilirubin peak                      | 9.2 mg/dL     | 0.0–0.3 mg/dL                 |
| Alkaline phosphatase peak                  | 448 U/L       | 40–129 U/L                    |
| Blood urea nitrogen baseline               | 28 mg/dl      | 6–24 mg/dL                    |
| Blood urea nitrogen peak                   | 171 mg/dl     | 8–24 mg/dL                    |
| Creatinine baseline                        | 1.22 mg/dL    | 0.6–1.2 mg/dL                 |
| Creatinine peak                            | 8.22 mg/dL    | 0.6–1.2 mg/dL                 |

Extensive immunological workup showed no evidence of consumption of complement, cryoglobulinemia, or a combination of clinical signs and symptoms along with serological workup, suggestive of rheumatological disease. There was an absence of a monoclonal spike on serum protein electrophoresis. Dermatological evaluation revealed a non-specific erythematous rash not suggestive of any infectious etiology, drug rash, vasculitis, or autoimmune disease. No biopsy was performed, and the rash faded away without specific treatment. An increase in inflammatory markers with a bilinear decrease in cell lines, along with decreased reticulocyte count was suggestive of bone marrow suppression in response to an inflammatory process that resolved spontaneously as the clinical condition improved. Mild abdominal lymphadenopathy and mild splenomegaly were benign processes. Hemophagocytic lymphohistiocytosis was also considered but given the clinical improvement during serial follow-up, this was thought to be unlikely and bone marrow biopsy was not performed. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) was considered unlikely after the application of the registry of severe cutaneous adverse reactions scoring system.

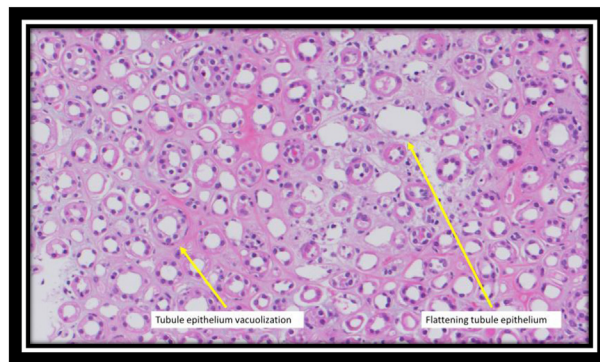


Fig. 3. Kidney Biopsy: Shows flattening or vacuolization of epithelium consistent with acute tubular injury. In the background we see multifocal interstitial inflammation with mononuclear cells, neutrophils, and eosinophils. There is mononuclear cell tubulitis consistent with acute interstitial Nephritis.

Initial broad-spectrum antibiotics were deescalated to empiric doxycycline for a 10-day duration. 1/3 blood cultures were positive for coagulase-negative staphylococcus, which was categorized as a contaminant. SARS-CoV-2 nucleocapsid antibody was positive, consistent with a previous SARS-CoV-2 infection, however serial PCR testing remained negative throughout the hospitalization.

On the fourth day of hospitalization the patient was extubated and was noted to have prolonged metabolic encephalopathy secondary to multi-organ failure with EEG, MR imaging of the brain and CSF results being insignificant. Due to AKI requiring dialysis a renal biopsy was performed showing diffuse Acute tubular necrosis (ATN) and multifocal interstitial nephritis likely due to a combination of sepsis, hypotension, and NSAIDs (Fig. 3). The patient was initiated on a prednisone course with taper along with trimethoprim/sulfamethoxazole for pneumocystis jirovecii prophylaxis and his renal function eventually made a full recovery. IVIG were contraindicated due to myocardial dysfunction.

An extensive workup for multiple etiologies was negative, and hence a diagnosis of exclusion, MIS-V was made. The latter satisfies the CDC criteria and recently reported level 1 Brighton collaboration network for case definition of MIS-A/MIS-V.<sup>1,12</sup> This severe adverse event following immunization was then reported to the United States Centers for Disease Control and Prevention (CDC).

### 3. Discussion

In a population-based surveillance study investigating adverse effects of mRNA vaccine using insurance company and electronic health records of patients in the USA, only six cases of MIS-V were

reported, when follow-up limited to 21 days post-vaccination was made after almost 12 million vaccine doses.<sup>9</sup> Based on national passive surveillance data in the USA, the CDC published a report highlighting the characteristics and outcome of 20 patients with MIS-A and 7 cases of MIS-V in adults between December 2020 and April 2021.<sup>13</sup> Patients demonstrated both a spike and nucleocapsid antibody after natural infection; this may however remain negative in mild cases in younger individuals or when PCR tests are falsely positive.<sup>13,14</sup> Notably, all seven cases of MIS-V in adults had a prior history of SARS-CoV-2 infection or serological evidence of nucleocapsid antibody presence.<sup>13</sup> More than 547 million doses of SARS-CoV-2 vaccine have been administered in the United States as of 15 February 2022[U.S. Department of Health & Human Services, 2022 #207], with only very few cases of MIS-V reported in the five months of passive surveillance. Most of them have likely come to attention due to the severity of the illness, requiring ICU level support.<sup>13</sup> Although deaths have been reported,<sup>15</sup> these are exceedingly rare, and vaccination continues to be encouraged, as there is no direct evidence that the vaccine alone causes MIS without a previous natural infection.<sup>13,15</sup>

MIS-C/MIS-A/MIS-V are diagnoses of exclusion. After other causes were excluded, positive nucleocapsid antibody test could provide evidence for a MIS-A diagnosis, but the patient never had signs of infection.<sup>16</sup> The only reported close contact exposure was seven months before presentation. To our knowledge, this is the first clinically descriptive case of MIS-V secondary to the use of Moderna mRNA-1273 vaccine in medical literature in an individual over 50 years of age. Like MIS-C and MIS-A, we still do not know the underlying pathophysiology of this syndrome. Various theories such as a dysregulated immune response to the vaccine with prior sensitization to SARS-CoV-2 infection leading to antibody-mediated cytokine storm, provoking autoimmunity have been proposed. Our patient had no prior autoimmune reactions. Corticosteroids and other immunomodulators can be used in MIS-V although these measures remain unproven.<sup>1,3,7,10,12,13,17</sup> In our case, steroid treatment effectiveness remains inconclusive, as its initiation did coincide with potential spontaneous recovery from ATN.

This case highlights the possible serious adverse reactions to the COVID-19 vaccine. These reactions require further research investigating pathophysiological, acute, and long-term sequelae, and potential therapeutic options. The challenge for the future will be formulating diagnostic criteria, correctly identifying MIS-V, and differentiating it from MIS-

A;<sup>4,5</sup> such differentiation is important for research aimed at optimal clinical management.

#### 4. Conclusion

MIS-V is a novel disease entity increasingly recognized during the course of the SARS-CoV-2 pandemic. The pathophysiology, risk factors, and management of this syndrome is a matter of ongoing research. Raising awareness is crucial to diagnosing this syndrome of exclusion.

#### Learning points

- 1) MIS has been described in children, adults and is now also being increasingly recognized as a rare complication in individuals receiving COVID-19 vaccination. The exact pathophysiology underlying this clinical syndrome remains unknown and is a matter of intense clinical research.
- 2) Emphasis is to be laid on clinical awareness and recognition, ruling out other differential diagnoses followed by good supportive therapy, often in an ICU, yielding favorable clinical outcomes. There has been some role for corticosteroids and IVIG, especially in children
- 3) Reporting and surveillance post-immunization needs to be robust in order to document the incidence and guide the public opinion and policymakers.
- 4) MIS-V likely occurs in individuals' post-vaccination who are already primed immunologically with prior SARS-COV-2 infection.

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#### Conflict of interest

The authors report there are no competing interests to declare.

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