SARS-CoV-2-Associated Multisystem Inflammatory Syndrome in Adults (MIS-A): a multicenter case series

Jose Ricardo Trigueros, MD[1*], Danielle L. Pannebaker, MD[2*], Travis A. Denmeade, MD[1], Brian D. Tran, MD[2], Matthew C. Russell, MD[2], Zachary Lubline, MD[2], Ryan C. Maves, MD[1,2], Catherine M. Berjohn, MD, MPH[2]

[1] Section of Infectious Diseases, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA
[2] Division of Infectious Diseases, Naval Medical Center, San Diego, California, USA
[*] Contributed equally.

Background

The first reports of SARS-CoV-2 associated Multisystem Inflammatory Syndrome in Children (MIS-C) were described in April 2020 followed by Multisystem Inflammatory Syndrome in Adults (MIS-A) in June of 2020. The case definition was last defined by CDC in October 2021. [1]

MIS-A continues to be an incompletely understood syndrome, it is believed to be the result of a variable and dysregulated immune response to SARS-CoV-2 through multiple mediators of inflammation driving organ injury instead of direct viral toxicity [2]. It frequently presents with a variety of symptoms including fevers, cardiovascular, gastrointestinal, mucocutaneous, and neurologic involvement that can mimic a multitude of infections and sepsis . Predominantly occurs in previously healthy children and young adults disproportionately affecting individuals of African American, Hispanic and Asian descent. MIS represents one of the most significant and yet under-recognized clinical consequences of SARS-CoV-2 infection, and the lack of understanding of its pathophysiology and limited treatment guidelines makes this an important area of study.

We present a multi-center case series to further describe the clinical presentation and laboratory findings of MIS-A, the therapeutic approach, clinical progress and the indirect impact on antimicrobial stewardship and financial burden of delayed diagnosis and treatment of MIS-A.

***CDC MIS-A Case Definition:**
Patient ≥21 years, hospitalized for ≥24 hours, with no alternative diagnosis for the illness and the following:

I. Clinical Criteria
Subjective fever or documented fever (≥38.0 C) for ≥24 hours prior to hospitalization or within the first THREE days of hospitalization and at least THREE of the following. At least ONE must be a primary clinical criterion.
Primary clinical criteria
- -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.*
- -Rash AND non-purulent conjunctivitis

Secondary clinical criteria
- -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)*
- -Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
- -Abdominal pain, vomiting, or diarrhea
- -Thrombocytopenia (platelet count <150,000/ microliter)

II. Laboratory evidence
-Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin

Methods

- A **retrospective review** of patients admitted with **MIS-A** to Atrium Health Wake Forest Baptist Medical Center (Winston-Salem, North Carolina, USA) and Naval Medical Center San Diego (San Diego, California, USA) from **January 2020 to December 2021** was performed.
- 10 patients meeting CDC diagnostic criteria[1*] of MIS-A were included. Each patient was identified for inclusion by clinicians directly involved in their care, with secondary review from the study team for confirmation, followed by data collection from electronic health record after IRB approval. All patient information was de-identified and only accessible to the PI and study investigators.
- Relevant clinical data including demographics, presenting symptoms, SARS-CoV-2 testing (PCR and serology), clinical support measures, and pertinent laboratory findings including inflammatory markers, and imaging were collected.
- A case-by-case assessment of medical interventions including antimicrobials, vasopressors, steroids, IVIG, RRT, artificial life support, vaccination status and days of hospitalization was performed. Data was analyzed to characterize the spectrum of presentation of MIS-A and its clinical progression.

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Results

- Male to Female Ratio: **7:3**
- Racial Distribution: **40% AA, 40% Hispanic, 20% Caucasian**
- Average time to admission from confirmed/suspected primary infection: **31 days**.

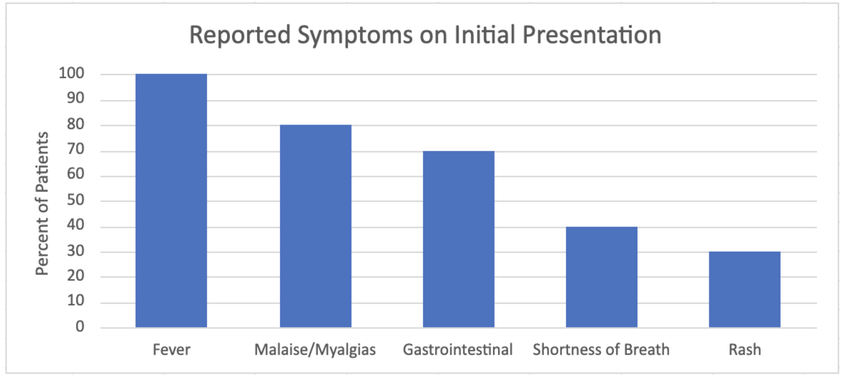
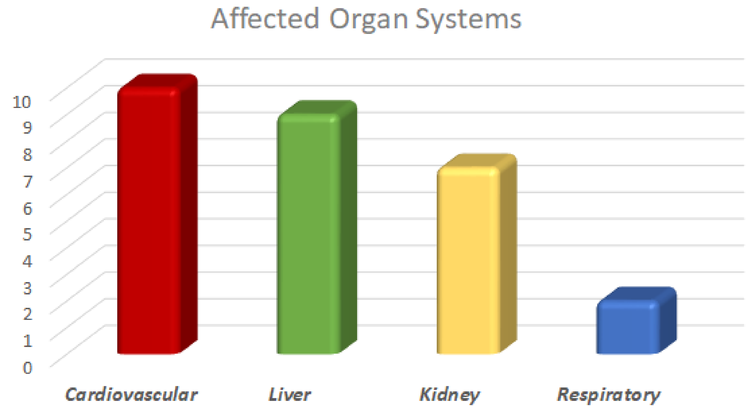


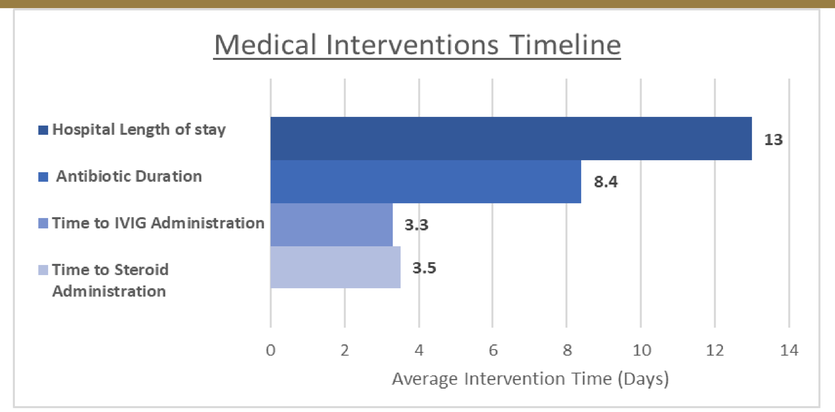
Table 1. Demographics

Gender	Number	Percent
Male	7	70%
Female	3	30%
Age Distribution	**Number**	**Percent**
18-25	5	50%
26-35	2	20%
36-45	1	10%
46-55	2	20%
Race Distribution	**Number**	**Percent**
African American	4	40%
Caucasian	2	20%
Hispanic	4	40%
Race-Gender Distribution	**Number**	**Percent**
African American Men	4	40%
African American Women	0	0%
Caucasian Men	1	10%
Caucasian Women	1	10%
Hispanic Men	2	20%
Hispanic Women	2	20%



MIS-A Targeted Interventions	Cases (n=10)	Avg Time to Initiation (Days)	Average Duration (Days)
Antibiotics	10	1	8.4
Intravenous Immunoglobulin	3	3.3	1
Previous COVID-19 Vaccination	1	N/A*	N/A*
Remdesivir	1	7	5
Steroids	8	3.5	8.4
Life Support Interventions	**Cases (n=10)**	**Avg Time to Initiation (Days)**	**Average Duration (Days)**
CRRT or Hemodialysis	1	6	9
Extracorporeal Membrane Oxygenation (ECMO)	1	5	5
Mechanical Ventilation	2	1.5	10
Vasopressor support	6	2	4.5

N/A *Vaccines were not widely available to the public during the studied period, only 1 patient in the series was vaccinated.



Discussion

Our case series findings appear to be congruent with previously published literature including Patel et al [3] and Davogustto et al [4] providing some of the most extensive and well described clinical findings and characteristics of this rare but increasingly identified entity. Our findings provide further evidence that MIS-A is most common in young male adults between 20-30 years of age of African American and Latino descent. [5]

Although the pathophysiology continues to be incompletely understood, current evidence suggests that MIS-A and MIS-C are the result of a variable and dysregulated immune response to SARS-CoV-2, with autoimmunity and mediators of inflammation driving organ injury instead of direct viral toxicity. [2]

To date, therapeutic approaches have been primarily guided by expert opinion centered on established immunomodulatory treatments for other inflammatory syndromes, such as Kawasaki Disease. Initial observational studies optimistically reported that immunomodulation, particularly with IVIG, may curtail the inflammatory state seen in MIS-C [6,7,8]. Similarly, MIS-A patients have demonstrated clinical responses to combinations of IVIG, high dose steroids, and immunomodulatory therapy. [9,10,11,12]

Throughout the pandemic, clinicians have honed their practice patterns, having become more adept at recognizing and treating myriad COVID-19 syndromic presentations quickly. With the publication of data on immunomodulatory agents in MIS as previously mentioned, it is presumed that this would have become a more frequent and earlier intervention in our MIS cases. However, that was not apparent in our case series across two institutions and may have confounded any trends in outcomes we had hoped to observe. This observation highlights the need for further characterization through large cohorts and registries for both retrospective and later prospective evaluation in order to establish a rapid identification of this entity as well as evidence-based guidelines with regard to optimal selection, duration, and impact of immunomodulating therapies.

Conclusion

MIS-A is a challenging complication of COVID-19 infection. Future studies evaluating treatment modalities including steroids, IVIG, antivirals, and monoclonal antibodies as well as the impact of vaccination are critical for prevention of patient morbidity and mortality. Growing evidence highlights the need for provider education for improved recognition of this syndrome. There is a need for an increased index of suspicion for MIS which may reduce delays in care, complications and long-term sequelae, inappropriate antimicrobial use, as well as direct and indirect health care costs.

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