

## Review Article

# Multisystem Inflammatory Syndrome in Children and Adolescents Associated with COVID-19: Review

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## INFO

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## ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized multiorgan disease seen in children, adolescent and young adults presumed to be a delayed immune mediated complication of Corona virus 2 (SARS-CoV-2) infection leading to severe acute respiratory syndrome. MIS-C can be associated with life threatening organ dysfunction requiring complex multidisciplinary care. Early recognition is important in order to prevent complication and serious sequelae. Because it is a post infective complication, in most of the cases RT-PCR comes negative though antibodies to COVID-19 are positive. Although SARS-CoV-2 in children are generally mild and nonfatal, there is increasing evidence of MIS-C. Clinical and laboratory features of MIS-C are similar to those of Kawasaki disease like syndrome and Toxic Shock Syndrome. Pathophysiology of MIS-C is still unclear and mainly due to formation of autoantibody and immune complex which activates inflammation. Most of the MIS-C associated with COVID-19, need treatment with ionotropic agents and anticoagulants. The long-term outcome of MIS-C like coronary artery aneurysm formation remain unknown and needs close follow up.

**Keywords:** SARS-CoV2, MIS-C, Kawasaki Disease, RT-PCR, Interleukin 6 and Interleukin 18

## Introduction

In December 2019 a number of Pneumonia cases were first reported in Wuhan, China. Later it was detected as COVID-19 pandemic, caused by SARS-CoV2. Children and adolescent comprise a small portion of COVID-19 cases. Pediatric cases account for 2.1-7.8% of confirmed COVID-19 cases as per statistics in Asia, Europe and North America.<sup>1</sup> Because most of the infections in children are asymptomatic and mild, the actual disease burden among children are underdiagnosed.

There have been increasing reports of COVID-19 associated multi inflammatory conditions which seems to develop after the infection rather than during the acute stage of COVID-19. The clinical features of these pediatric cases are similar to other inflammatory syndromes like Kawasaki disease Shock syndrome and Toxic Shock syndrome.<sup>2</sup> MIS-C can lead to shock and multiple organ failure requiring intensive care. As per WHO a case definition of MIS C includes clinical presentation, elevated inflammatory markers, evidence of



infection or contact with patients who are COVID-19 with exclusion or other microbial causes of infections.<sup>3</sup>

### **COVID-19 Causes and Link with MIS-C**

Children infected with SARS CoV2 developing severe disease depends upon age, viral load and chronic co-morbidities.<sup>4</sup> Children younger than 1 year are at higher risk of developing COVID-19 although these infections are infrequent.<sup>5</sup> After 1<sup>st</sup> year of life patients appear to be asymptomatic or have milder symptoms.<sup>6</sup> Data suggest a genetic locus partly associated with more severe disease<sup>7</sup> and some ethnic group (e.g Africans) might have strong association with MIS C.<sup>8</sup> In the current COVID-19 pandemic there has been increasing cases of an inflammation illness occurring in children 4-6 wks after the peak of COVID-19 infection infections in the affected populations.<sup>9</sup>

### **COVID-19 Pathophysiology and Link with MIS-C**

The β Corona virus includes SARS CoV, SARS CoV2 and MERS. SARS CoV2, like other Corona viruses, is transmitted from infected individuals, through contaminated surfaces by droplets while coughing and sneezing. The virus enters a cell by binding to Angiotensin converting enzymes II which is highly expressed in lung cells, alveolar cells, cardiac myocytes and vascular endothelium.<sup>10</sup> Evidence has shown that a dysregulated innate immune response and subsequent cytokine storm leading to endothelium damage<sup>11</sup> might play a role in clinical manifestation in severe COVID-19 cases, leading to acute lung injury, Acute respiratory distress syndrome and multiple organ failure. Neutrophils play a major role in immune response through formation of Neutrophil Extracellular Trap (NETs).<sup>12</sup> This process is called as NETosis which is stimulated by many viruses. Their main function is to trap the virus but it can trigger inflammatory and immunological reaction in an uncontrolled manner.

Only a third of reported MIS-C cases are positive by RT-PCR SARS-CoV2, whereas most cases are positive with an antibody test indicating past infection. The delay in presentation and low positive RT PCR with high antibody titer suggest that this inflammatory syndrome is not mediated by direct invasion but with the development of acquired immune response to SARS CoV2. In a study reported by Gruber and colleagues<sup>13</sup> patients with MIS-C had neutralizing antibodies against SARS CoV2 which are associated with Interleukin-18 (IL-18) and IL-16 activation, myeloid chemotaxis and activation of Lymphocytes, Monocytes and Natural killer cells. The inflammatory disorders triggered by SARS Cov2 have features similar to Kawasaki disease and can also result in Coronary Aneurysms. The virus might act as the immune trigger and cause injury to the heart and coronary arteries. The development of T cells responses to SARS CoV2 might play a role in organ

damage and inflammatory process.

The mechanism in SAS CoV2 acquired immune response include:

- Antibody or T cell recognition of self-antigens resulting in autoantibodies
- Antibody or T cell recognition of virus antigens expressed in infected cells
- Formation of immune complexes which activates inflammation
- Viral superantigens sequences which activate host immune cells

### **Management of MIS-C**

If MIS-C is suspected or diagnosed, a multidisciplinary team approach should be taken. Supportive care is crucial with special attention to vital organs, hydration, electrolytes and metabolic status.

#### **Role of Antiviral Drugs**

Remdesivir decrease viral RNA production so shorten illness duration in adults however most children with MIS-C are not in acute phase of illness and are RT PCR negative, hence the role of Remdesivir is limited.

#### **Role of Steroids**

Administration of low dose dexamethasone to patients with MIS-C could be beneficial to suppress the immune response and subsequent inflammatory disorders. Other steroids like methyl prednisolone and Prednisolone become extremely used for MIS-C.

#### **Prevention and Treatment of Coagulopathy**

Many children with MIS-C have elevated D-Dimers which is used as a guide for giving anticoagulants. Low dose aspirin antiplatelet therapy are generally recommended. It should be given when follow up echocardiogram excludes coronary artery aneurysm or injury. Although mechanisms underlying the coagulopathy in COVID-19 is still unknown, anticoagulant therapy is recommended for patients with severe disease.<sup>14</sup>

#### **Cardiac Assessment**

Arrhythmia, Myocardial injury also been detected by ECG in some cases of MIS-C.<sup>15</sup> Coronary Artery Aneurism (CAA) might develop after discharge from hospital. Many patients present with significantly elevated troponin which indicates myocardial injury that leads to arrhythmia and left ventricle dysfunction.<sup>16</sup>

#### **Management of Hypotension**

Usually children with MIS-C present with hypotension and signs of shock. These patients should be treated with volume expansion. Hypotension in children with MIS-C is often fluid resistant and should be managed with vasopressor

like Epinephrine and Norepinephrine. Dobutamine can be used in severe myocardial dysfunction. Broad spectrum antibiotics can be used if high C-Reactive Protein or increase in neutrophil count. Most children with MIS-C do not require respiratory support May Need intubation and extracorporeal membrane oxygenation because of cardiovascular collapse<sup>17</sup>. Children can be discharged from the hospital after their inflammatory markers are normalized, they remain afebrile, normotensive, well hydrated and not requiring oxygen supplement.

## Conclusion

SARS-CoV2 virus and its association with multisystem inflammatory syndrome in pediatric patients has only few scientific evidences. Although there is evidence that development of MIS-C is a post viral immunological reaction to COVID-19. It has to be established whether patients with fever and inflammation due to SARS-CoV2 progress to Kawasaki disease shock or organ failure if left untreated. Another question includes whether severity of the disease progression and prognosis varies at different stages of childhood and adolescence. Clinical management and treatment protocol should be tested in randomized controlled trials to compare clinical outcomes and changes in inflammatory markers.

**Conflicts of Interest:** None

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