**Hypothesis**

# Etiology Scenarios for Multisystem Inflammatory Syndrome in Children and Adults Associated with SARS-CoV-2

**Darrell O. Ricke**

*Massachusetts Institute of Technology, Lincoln Laboratory, Lexington, MA 02420, USA*

## Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) and adults (MIS-A) is associated with SARS-CoV-2 infection with unknown pathogenesis. I propose that high SARS-CoV-2 antibody levels are contributing to hyper-activated mast cells driving disease pathogenesis. Multiple scenarios that result in sufficiently high antibody levels are proposed including ongoing persistent infections, subsequent infections associated with secondary antibody immune responses, etc. Candidate adjunctive therapy treatments are proposed based on COVID-19 patients efficacy responses to treatments targeting activated mast cells and virus elevated prostaglandin-endoperoxide synthase 2 (PTGS2)/cyclooxygenase-2 (COX-2) levels.

**Keywords**: MIS-C, MIS-A, Multisystem inflammatory syndrome, Mast cells

## List of Abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus Disease 19 |
| COX-2 | Cyclooxygenase-2 |
| IgG | Immunoglobulin G |
| KD | Kawasaki Disease |
| matAbs | maternally transferred antibodies |
| MIS-A | Multisystem Inflammatory Syndrome in Adults |
| MIS-C | Multisystem Inflammatory Syndrome in Children |
| NF-κB | nuclear factor kappa B |
| $PGE_2$ | prostaglandin E2 |
| PTGS2 | prostaglandin-endoperoxide synthase 2 |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| TACE | (TNF-α)-converting enzyme |
| TNF-α | Tumor Necrosis Factor alpha |

## Introduction

Individuals infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus can be asymptomatic [1], can develop COVID-19 [2], and/or can develop Multisystem Inflammatory Syndrome in Children (MIS-C) [3] or Adults (MIS-A) [4]. MIS-C and MIS-A are conditions where different body parts can become inflamed, including: heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs [5]. Previously, I proposed that hyper-activated mast cells are responsible for MIS-C associated with first infections for infants with maternally transferred antibodies (matAbs) and second infections for children [6]. This hypothesis posits that MIS-C and MIS-A are caused by high titer SARS-CoV-2 antibody/antigen complexes binding to mast cell Fc receptors. Such binding would be expected to trigger mast cell hyper-activation with subsequent release of histamine and inflammatory molecules. Herein, I refine this model by examining additional etiology scenarios for the development of MIS-C and

**\*Corresponding Author:** Darrell O. Ricke, MIT Lincoln Laboratory, Group 23, Lexington, MA 02421, USA, Email: Darrell.Ricke@ll.mit.edu

*Citation: Darrell O. Ricke (2021). Etiology Scenarios for Multisystem Inflammatory Syndrome in Children and Adults Associated with SARS-CoV-2*

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MIS-A driven by high SARS-CoV-2 antibody titers. In this model, MIS-C and MIS-A are considered as being the same disease. In summary, high SARS-CoV-2 antibody titers are proposed to be hyper-activating mast cells with release of histamine and inflammatory molecules inducing capillary vasoconstrictions in MIS-C and MIS-A patients.

## Hypothesis

I propose that MIS-C and MIS-A are triggered by hyperactivated mast cells associated with SARS-CoV-2 infection (Figure 1). I propose that MIS-C and MIS-A are triggered by SARS-CoV-2 antibodies levels exceeding a threshold that is high than normal primary immune response level.

## Etiology Models of MIS-C and MIS-A

MIS-C has been proposed to be a variant of Kawasaki Disease (KD, previously called disease of unknown cause which has been associated with multiple pathogens [7-30]. Previously, I proposed that KD and MIS-C are mast cell diseases with MIS-C a KD variant associated with SARS-CoV-2 infection [6]. There are specific groups of children at risk for development of MIS-C. The first involves infants with matAbs to SARS-CoV-2 which develop MIS-C on initial infection (Table 1, etiology scenario 1) [6]; a



**Figure 1**. Mast cells releasing histamine and inflammatory molecules in MIS-C and MIS-A patients hyper-activated by Fc receptors binding high titer SARS-CoV-2 antibodies binding to SARS-CoV-2 viruses.

nine-month old infant with MIS-C is consistent with this etiology scenario [31]. The second MIS-C risk group are children with a second SARS-CoV-2 infection (Table 1, etiology scenarios 2 & 3) [6]. Consistent with these scenarios, children with a previous COVID-19 infection were found to develop MIS-C upon apparent reinfection [32-36]. The trigger threshold for KD, MIS-C, and MIS-A for level of hyper-activating mast cell antibodies may be higher than reached by a typical primary immune response.

It may be possible for some individuals to develop MIS-C or MIS-A as part of an ongoing persistent SARS-CoV-2 infection (Table 1, etiology scenario 4). Upon initial infection, individuals develop a primary antibody response to SARS-CoV-2 with IgG peaking about day 49 after illness onset [37]. For MIS-C and MIS-A, this extended primary antibody response may contribute to hyper-activation of mast cells if the SARS-CoV-2 infection persists within an individual that generates high titer SARS-CoV-2 antibody responses. Persistent SARS-CoV-2 viral infections have been reported [38-41]. Mast cells with Fc receptor bound SARS-CoV-2 antibodies may be responding to persistent virions. Some children are developing MIS-C after COVID-19 from a possible persistent infection [42,43]. Multiple children with MIS-C have been identified as having significant SARS-CoV-2 antibody titers at the time of hospital admission [44]. Multiple children suffering MIS-C have previously had COVID-19 [32-34], had prior family exposures to SARS-CoV-2 [45, 46], or have evidence of prior SARS-CoV-2 infection [45-47]. Likewise, a woman with MIS-A tested positive for SARS-CoV-2 antibodies suggesting prior infection [48]. In support of these etiology scenarios, all MIS-C children in 2 studies (n=10, each) had high SARS-CoV-2 IgG antibody titers [49, 50]. MIS-C patients can also have detectable immunoglobulin M antibodies, indicating recent SARS-CoV-2 infection [49]. MIS-C and MIS-A onset of symptoms coincides with either a second SARS-CoV-2 infection or an ongoing persistent infection; these scenarios support the hypothesis that there may be an onset threshold for disease above that of a normal primary immune response.

Gastrointestinal symptoms are reported in a majority of MIS-C patients [44,51-54]; this may indicate possible ongoing SARS-CoV-2 persistent infections in the gastrointestinal tract. A MIS-A patient with profound gastrointestinal symptoms has also been reported [55]. MIS-C is developing in some children with COVID-19 and persistent SARS-CoV-2 infections [56]. Some COVID-19 patients are developing cross-reactive antibodies [57] (likely from prior exposure to a different coronavirus).
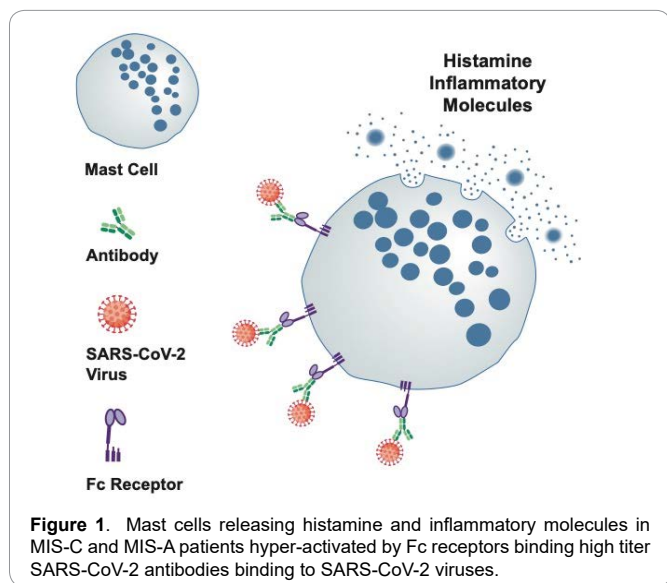
**Table 1**. Five etiology scenarios in which MIS-C and MIS-A patients developed high titer SARS-CoV-2 antibodies hyper-activating mast cells when bound to mast cell Fc receptors and SARS-CoV-2 viruses: (1) at risk infants with maternally transferred antibodies SARS-CoV-2 and initial SARS-CoV-2 infection [6], (2) at risk patients with existing memory B cells primed by initial SARS-CoV-2 infection (asymptomatic COVID-19) generating high SARS-CoV-2 secondary antibody response on subsequent infection [6], (3) at risk patients with existing memory B cells primed by initial SARS-CoV-2 infection (COVID-19 with symptoms) generating high SARS-CoV-2 secondary antibody response on subsequent infection [6], (4) at risk patients with persistent SARS-CoV-2 infection and extended (higher) primary antibody response, and (5) at risk patients with high cross-reactive (secondary) antibody response on initial SARS-CoV-2 infection.

| At Risk Group | Phase 1 - Initial Antibody Response | Phase 2 - SARS-CoV-2 antibodies hyperactivating mast cells |
|---|---|---|
| 1 – Infants [6] | Mother antibodies to SARS-CoV-2 | Infant with preexisting SARS-CoV-2 matAbs and first SARS-CoV-2 infection |
| 2 - Patients[6] | First SARS-CoV-2 infection with primary antibody response: asymptomatic COVID-19 | Second SARS-CoV-2 infection with high secondary antibody response |
| 3 - Patients[6] | First SARS-CoV-2 infection with primary antibody response: COVID-19 with symptoms | Second SARS-CoV-2 infection with high secondary antibody response |
| 4 - Patients | First SARS-CoV-2 infection with primary antibody response | Persistent SARS-CoV-2 infection with higher extended primary antibody response |
| 5 - Patients | Non-SARS-CoV-2 coronavirus infection | First SARS-CoV-2 infection with high titer cross-reactive (secondary) antibody response |

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Individuals with initial SARS-CoV-2 infection coupled with high titer secondary cross-reactive antibody responses would be at risk to develop MIS-C and MIS-A (Table 1, etiology scenario 5); there have been no reported case reports consistent with this scenario. The etiology scenarios for the development of MIS-C in infants, MIS-C in children, and MIS-A in adults are summarized in Table 1 for high titer SARS-CoV-2 antibodies hyper-activating mast cells when binding SARS-CoV-2 viruses and mast cell Fc receptors (Figure 1).

## Mast cell hyper-activation and candidate adjunctive therapy treatments

The SARS-CoV-2 virus may have at least two pathways for contributing to hyper-activation of mast cells. First, based on sequence similarity to SARS-CoV-1, it has been hypothesized that the SARS-CoV-2 nucleocapsid protein can bind to the COX-2 promoter to upregulate COX-2 and COX-2-dependent proinflammatory lipids, including prostaglandin E2 ($PGE_2$) [58,59]. Second, the SARS-CoV-1 Spike protein interacts with Tumor Necrosis Factor alpha (TNF-α)-converting enzyme (TACE) inducing TNF-α production [60]; the nuclear factor kappa B (NF-κB) pathway is activated by inducing I-κBα degradation [61]. TNF-α stimulates PTGS2/COX-2 expression [62] resulting in elevated levels of prostaglandin $E_2$ ($PGE_2$) [63]. Elevated levels of $PGE_2$ can cause hyper-activation of mast cells, leading to degranulation and release of histamine and inflammatory mediators [64]. The SARS-CoV-2 Spike protein may have a similar interaction with TACE. Treatments, including celecoxib [58,63,65], famotidine [58,65,66], cetirizine [67], dexchlorpheniramine [67], and montelukast [68] are exhibiting possible efficacy in COVID-19 patients by targeting mast cells and COX-2; these treatments may provide additional benefit to MIS-C and MIS-A patients supplementing current treatment protocols.

## Conclusions

MIS-C and MIS-A are proposed to develop with high titer SARS-CoV-2 antibodies bound to mast cells on second infection [6] or upon initial infection with extended higher primary antibody response and persistent infection (proposed herein), initial infection with cross-reactive higher secondary antibody response (proposed herein), or matAbs for infants upon initial infection [6]. Observed MIS-C and MIS-A symptoms are consistent with localized elevated levels of histamine, inflammatory molecules, and vasoconstrictions. In these etiology scenarios, infected individuals may be asymptomatic or have COVID-19 on first infection. The prerequisites of either a subsequent infection or persistent infection are also consistent with reduced incidence of MIS-C and MIS-A compared to COVID-19. The etiology scenarios for extended primary antibody response with persistent infection and second infection are consistent with observed delayed onset of MIS-C and MIS-A following surges in SARS-CoV-2 infections. The etiology scenarios presented are consistent with onset of MIS-C in infants and children, and also MIS-A in adults. Candidate adjunctive therapy treatments are proposed based on observed efficacy responses in COVID-19 patients targeting activated mast cells and virus induced COX-2 overexpression. These etiology scenarios can help inform protective health care measures together with proposed adjunctive therapy treatment candidates in response to the increasing numbers of MIS-C and MIS-A patients being observed as the COVID-19 pandemic continues.

## Conflicts of Interest

None.

## Data Availability Statement

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

## Consent statement/Ethical approval

Not required

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