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## Multisystem Inflammatory Syndrome in Children (MIS-C) Linked to COVID-19

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### ABSTRACT

Covid 19 Virus has created havoc all over the world. As of today, about 165 million people are diagnosed with this deadly virus resulting in about 3.5 million deaths. The developed countries are also not spared from this virus. The second wave of Coronal virus is now spreading in many countries and country like India has much of the impact. Developing nations find it extremely difficult to cope up with the huge infrastructure requirement in the health sector due to a large number of people falling sick due to COVID 19. The risk of severe complications and death has been highest among older people and in persons with underlying noncommunicable diseases (NCDs), such as hypertension, cardiac disease, chronic lung disease, and cancer.<sup>1-4</sup> Limited data describe clinical manifestations of COVID-19 that are generally milder in children compared with adults,<sup>5-8</sup> but also show that some children do require hospitalization and intensive care. As the entire world is battling against the deadly COVID novel coronavirus, there seems to be another disease that has proved to be fatal when left unattended in some children post COVID-19. That is Multisystem inflammatory syndrome in children (MIS-C) or Paediatric Inflammatory multi-system syndrome (PIMS). Reports from Europe and North America have described clusters of children requiring admission to intensive care units with a multisystem inflammatory condition. Case reports have described acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock.<sup>12-14</sup> Initial hypotheses are that this syndrome may be related to COVID-19 based on initial laboratory testing. Children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids.

## **INTRODUCTION**

Multisystem inflammatory syndrome in children (MIS-C) is a serious condition that appears to be linked to coronavirus disease 2019 (COVID-19). Due to MIS-C body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. Signs and symptoms depend on which areas of the body are affected. Children with MIS-C may have a fever and various symptoms, including abdominal (gut) pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes, or feeling extra tired. One of the initial challenges clinicians were facing was differentiating patients with MIS-C Vs Kawasaki disease or Toxic shock syndrome.

MIS-C is not a disease but considered a syndrome that has a group of signs and symptoms, but its cause and risk factors are still unknown. More clinical data of children who have MIS-C may lead to eventually find a cause for this syndrome.

In rare cases, it is reported that some adults too developed signs and symptoms similar to MIS-C. Multisystem inflammatory syndrome in adults (MIS-A), occurs in adults who were previously infected with the COVID-19 virus and many are not aware of it. MIS-A seems to occur weeks after COVID-19 infection, though some people have a current infection. If MIS-A is suspected, a diagnostic or antibody test for COVID-19 can help confirm current or past infection with the virus, which aids in diagnosing MIS-A.

MIS-C is rare, and most children who have it eventually get better with medical care. But some kids rapidly get worse, to the point where their lives are at risk.

### **Causes**

The exact cause of MIS-C is not known yet, but it appears to be an excessive immune response related to COVID-19. Many children with MIS-C have a positive antibody test result. This means they've had a recent infection with the COVID-19 virus. Some may have a current infection with the virus. Identifying and studying more children who have MIS-C may help to eventually find a cause.

### **Pathogenesis**

Early infection (phase I) with SARS-CoV-2 is likely to be asymptomatic or mildly symptomatic in children. The pulmonary phase (phase II) is severe in adults but is mild or absent in many children. The early infection appears to trigger macrophage activation

followed by the stimulation of T-helper cells. This in turn leads to cytokine release, the stimulation of macrophages, neutrophils, and monocytes, along with B-cell and plasma cell activation with the production of antibodies leading to a hyperimmune response (stage III). This immune dysregulation is associated with inflammatory syndrome in affected children. Direct infection with SARS-CoV-2 is less likely to play a role in MIS-C.<sup>16</sup>

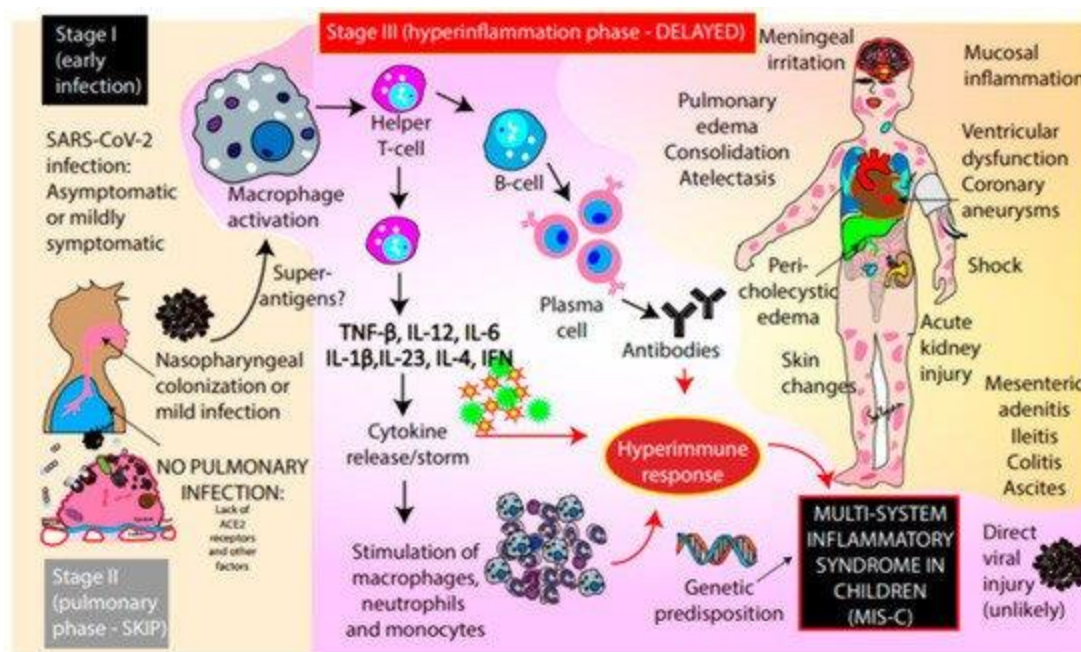


Figure No. 1: Pathogenesis

### Risk factors

Studies are needed to help determine why MIS-C affects children more often than others. Factors may include, for example, differences in access to health information and services as well as the possibility of risks related to genetics. Most children with MIS-C are between the ages of 3 and 12 years old, with an average age of 8 to 9 years old. Some cases also seen occurred in older children and infants as young as 8 months old in some countries. As India is seeing a sharp spike in the number of children testing positive for COVID-19 infection in the past 2 months there is a greater chance of MIS-C diagnosing in more children. In rare cases, children can suffer from MIS-C which develops 2 to 3 weeks after recovering from COVID-19.

## Symptoms

Symptoms are still being documented because the illness is so new. Not all children have the same symptoms, general signs and symptoms of the multisystem inflammatory syndrome in children (MIS-C) are as given below.

**The main symptom to watch for is a persistent fever, that lasts for more than 24 hrs and usually present for several days with fatigue and loss of appetite or not drinking enough fluids.**

Specific features:-

- Rash or bilateral non-purulent conjunctivitis with bloodshot eyes
- Mucocutaneous inflammation signs (oral, hands, or feet), swelling of the lips and tongue, and bluish lips or face
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).
- Skin rash
- Feeling unusually tired
- Neck pain
- Fast heartbeat
- Shortness of breath
- Pain or pressure in the chest that doesn't go away
- Headache, dizziness, or lightheadedness
- Enlarged lymph nodes
- Hypotension or shock.

Persistent fever and Gastrointestinal symptoms are the most common symptoms.

Cardiac manifestations are common, including ventricular dysfunction, coronary artery dilation and aneurysms, arrhythmia, and conduction abnormalities. Severe cases can present as vasodilatory cardiogenic shock.

### **Emergency warning signs of MIS-C which requires immediate care**

- Severe stomach pain
- Difficulty in breathing
- Pale, gray, or blue-colored skin, lips, or nail beds — depending on skin tone
- Becoming Confused
- Inability to wake up or stay awake

If your child has any of the emergency warning signs listed above or is severely sick with other signs and symptoms get clinical care immediately. Take your child to the nearest emergency department.

If your child isn't severely ill but shows other signs or symptoms of MIS-C, contact your child's doctor right away for advice. Doctors may want to do tests such as blood tests, or imaging tests of the chest, heart, or abdomen to check for areas of inflammation and other.

### **Diagnosis/Evaluation**

Some children affected with MIS-C shows negative for a current infection with the COVID-19 virus. This means they don't currently have the virus that causes COVID-19. Yet evidence indicates that many of these children were infected with the COVID-19 virus in the recent past, as shown by positive antibody test results.

An antibody test with a positive result means that the child's immune system developed blood proteins (antibodies) that fought the COVID-19 virus. Sometimes this blood test is the only indication that the child was ever infected — meaning that the child may have fought the infection without ever having signs or symptoms of COVID-19. Still, some children with MIS-C are currently infected with the virus that causes COVID-19.

In addition to doing antibody testing and a clinical assessment, other lab evaluations may be suggested by doctors to assess for inflammation, blood clotting, liver function, heart function, and other signs of MIS-C:

### **Laboratory tests:**

- Pro-BNP,

- Triglycerides
- Creatine kinase
- Amylase,
- Blood and urine culture
- D-dimer
- Prothrombin time/partial thromboplastin time (PT/PTT)
- INR
- CRP
- ESR
- Ferritin
- LDH
- Comprehensive metabolic panel
- Fibrinogen



**Common laboratory findings in case reports have included:**

- Abnormal Fibrinogel
- Absence of potential causative organisms (other than SARS-CoV)
- High CRP
- High D-dimer
- High Ferritin
- Hypo Albuminemia
- Lymphopenia
- Thrombocytopenia

- Raised troponin
- Raised LDH
- Neutrophilia

#### **Imaging tests:**

- **Chest X-ray**-- Patchy symmetrical infiltrates, pleural effusion,
- **Echo and ECG**-- Myocarditis, Valvutis, Pericardial effusion, Coronary artery dilatation
- **Abdominal USS**—Colitis, Lymphadenopathy, Hepatosplenomegaly, Ascites

Inflammation can seriously affect the heart, blood vessels, kidneys, digestive system, brain, skin, or eyes.

When doctors suspect MIS-C, they need to rule out active cases of COVID-19 as well as other inflammatory conditions such as Kawasaki disease, sepsis, or toxic shock syndrome, for early diagnosis and proper treatment.

#### **Treatment**

Most children with MIS-C need to be treated in a hospital. Some need treatment in a pediatric intensive care unit. Treatment usually involves supportive care and measures to reduce inflammation in any affected vital organs to protect them from permanent damage. Treatment depends on the type and severity of symptoms and which organs and other parts of the body are affected by inflammation.

Clinicians who suspect MIS-C in a child should use a multidisciplinary approach involving many pediatric specialists, which may include but is not limited to cardiology, infectious disease, immunology, hematology, rheumatology, pediatric hospital medicine, and critical care, to guide individual patient treatment. Optimal treatment for a patient with MIS-C is not known; however, is best determined by the multidisciplinary clinical team. The following interventions have been used:

#### ***Supportive care may include:***

- Fluid resuscitation, if levels are too low (dehydration).

The fluid if infused is too much or too fast may intensify the leakage in the alveoli.<sup>15</sup>

- Oxygen to help to breathe.
- Blood pressure medications to normalize low blood pressure related to shock or to help with heart function.
- Respiratory support
- Medications that reduce the risk of blood clots, such as aspirin or heparin due to concerns for Coronary artery involvement.
- In very rare cases, extracorporeal membrane oxygenation (ECMO) using a machine that does the work of the heart and lungs.
- Other types of care

***Treatment includes:***

- **Antibiotics** are routinely used to treat potential sepsis.
- **Intravenous immunoglobulin (IVIG)**, a biologic medicine that contains immune system antibodies.

Patients with MIS-C are usually treated with IVIG, 2 grams/kg (max of 100 grams). Patient cardiac function and fluid status influence the duration of the infusion of IVIG therapy.

- **Steroid therapy** to help treat swelling or inflammation

Patients who do not improve clinically, or whose laboratory values do not improve, have also been treated with steroid therapy (ranging from 2 to 30 mg/kg/day of **methylprednisolone** depending on the severity of illness) and **biologics** (eg, anakinra, 2 to 10 mg/kg/day, subcutaneously or intravenously, divided every 6 to 12 hours).

A recent large observational study found that initial treatment with both IVIG and steroid therapy led to earlier resolution of fever compared to IVIG alone. Due to rapidly evolving treatment recommendations, consultation with pediatric subspecialists is strongly recommended.

If the patient has laboratory or imaging evidence of myocardial injury or findings concerning coronary artery aneurysms, discussion with pediatric cardiology is suggested before the use of steroids.



Patients treated with steroids and/or biologics often go home with a 3-week taper of steroids and/or biologics.

- All patients with MIS-C, unless there are contraindications (eg, platelets <100,000 or active bleeding), should be started on low-dose aspirin for thromboprophylaxis. Consultation with cardiology and hematology should take place to determine whether further intervention is required.

There is no evidence that MIS-C is contagious. But there's a chance that the child could have an active infection with the COVID-19 virus or another type of contagious infection. So the hospital will use infection control measures while caring for your child.

### **Complications**

Many specialists consider MIS-C to be a complication of COVID-19. Without early diagnosis and appropriate management and treatment, MIS-C can lead to severe problems with vital organs, such as the heart, lungs, or kidneys. In rare cases, MIS-C could result in permanent damage or even death.

### **Prevention**

The WHO recommends the following precautions for avoiding exposure to the virus that causes COVID-19<sup>15</sup>:

- **Vaccination.** Many countries have started clinical trials for vaccinating children below 18 years of age. In some countries, vaccination for 12 to 18 age is underway. A vaccine can prevent the child from getting the COVID-19 virus.
- **Keep hands clean.** Wash hands often with soap and water for at least 20 seconds. If soap and water aren't available, use a hand sanitizer that contains at least 60% alcohol.
- **Avoid people who are sick.** In particular, avoid people who are coughing, sneezing, or showing other signs that indicate they might be sick and contagious.
- **Practice social distancing.** This means that one child should stay at least 6 feet (2 meters) from other people when outside of your home.
- **Wear cloth face masks in public settings.** When in indoor public places or outdoors where there is a high risk of COVID-19 transmissions, such as at a crowded event or large

gathering, both you and your child — if he or she is at least 2 years old — should wear face masks that cover the nose and mouth.

- **Avoid touching your nose, eyes, and mouth.** Encourage your child to follow your lead and avoid touching his or her face.
- **Cover your mouth with a tissue or your elbow when you sneeze or cough.** You and your child should practice covering your mouths when you sneeze or cough to avoid spreading germs.
- **Clean and disinfect high-touch surfaces every day.** This includes areas of your home such as doorknobs, light switches, remotes, handles, countertops, tables, chairs, desks, keyboards, faucets, sinks, and toilets.
- **Wash clothing and other items as needed.** Wash laundry and plush toys as needed on the warmest setting as advised and dry them fully.

## CONCLUSION

The exact cause for this disease is yet to be known to the health care system. Till the scientific community comes up with proper findings, people should take extreme care to prevent COVID-19 in children. Multi inflammatory syndrome in children with COVID-19 has gone unnoticed but it is time we start talking about this “invisible killer” before things spiral out of control. This is only a humble attempt to pen to create awareness for what is an invisible killer called MISC-C, an incredibly serious condition directly related to COVID-19 and one that affects children post it.

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