COVID – 19 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): A REVIEW

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Abstract:
An association between a novel hyper inflammatory condition in children and SARS-CoV-2 was recently termed as multisystem inflammatory syndrome (in children) (MIS-C). MIS-C is a dangerous pediatric complication of COVID-19. MIS-C was originally identified as a unique life-threatening hyperinflammatory illness in April 2020. SARS-CoV-2 infection generally causes MIS-C to manifest 4-6 weeks later, suggesting that the virus may serve as a trigger in people with specific genetic predispositions. MIS-C is an inflammatory syndrome which can affect any organ system. The most common symptoms are fever and GI symptoms. Patients with MIS- C may also appear with an irregular ECG and an increase in inflammatory markers. Resuscitation is the first line of treatment, and point-of-care ultrasound is used to carefully identify whether the shock is cardiac or vasodilatory. In most cases, patients need to be admitted to an ICU. Treatment should include IV immunoglobulin, anticoagulation, and consideration of corticosteroids. For refractory cases Interleukin-1 and/or interleukin-6 inhibitors may be considered. Thus, Growing awareness of MIS-C, a disease linked to morbidity and death, as a potential consequence in young COVID-19 patients. It's crucial for emergency medical professionals to understand how to identify and manage this disease.

Keywords: Multisystem inflammatory syndrome, genetic predispositions, serological positivity, real-time polymerase chain reaction.

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INTRODUCTION:

Multisystem inflammatory syndrome in children (MIS-C) is an uncommon illness linked to COVID-19 that typically manifests 2–6 weeks after a kid contracts COVID-19. The child's SARS-CoV-2 infection could be undetectable if it has only very minor symptoms or none at all. [1] Various body parts, such as the skin, eyes, brain, heart, lungs, kidneys, skin, and gastrointestinal system, experience inflammation as a result of MIS-C. Even though MIS-C can be fatal, the majority of kids who are diagnosed with it recover with medical attention. Although the incidence of MIS-C worldwide is unknown, it seems to be uncommon. Children with COVID-19 had an overall incidence of 322 per 100,000 people, with MIS-C occurring in those under the age of 21 at a rate of 2 per 100,000. [2]

The COVID-19 illness is caused by the novel coronavirus that is now known as severe acute respiratory syndrome-coronavirus type 2 (SARSCoV-2), was initially identified in a patient on December 8, 2019, in the Chinese city of Wuhan. The COVID-19 virus frequently causes fever, coughing, exhaustion, and breathe problems. However, some sufferers go on to develop pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure whereas the majority of affected people have no or minimal symptoms. On January 30, 2020, the World Health Organisation (WHO) declared it a Public Health Emergency of International Concern. [3]. In children, COVID-19 appears to be less aggressive and has milder symptoms than in adults. Children most frequently experience a low fever, cough, rhinorrhea, and sore throat. Additionally possible are gastrointestinal issues including vomiting and diarrhoea.[4] The COVID-19 infection in children was either asymptomatic or mild, with only a small percentage needing hospitalisation and lower mortality than in adults. Children most frequently experience a low fever, cough, rhinorrhea, and sore throat. Additionally possible are gastrointestinal issues including vomiting and diarrhoea. The likelihood of a connection with SARS-CoV-2 was investigated when clusters of hyperinflammatory processes in children with atypical Kawasaki disease (KD) and shock were reported in many European countries in May 2020. Later, the cases were identified by the World Health Organisation (WHO) and the Centres for Disease Control and Prevention (CDC) as multisystem inflammatory syndrome in children (MIS-C) related with COVID-19. Uncommon but severe and perhaps fatal, MIS-C is a disease. The latter half of April 2020 saw the initial discovery of a rare condition in children and adolescents called as "Multisystem Inflammatory Syndrome in Children" (MIS-C) that may be related to SARS-CoV-2 infection. New York and other American locations came after the UK and Italy, where the initial claims first surface. According to preliminary reports, this syndrome's symptoms are similar to those of well-known conditions like Secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome, toxic shock syndrome, and Kawasaki disease [5].

IMPORTANCE OF COMPARING MIS-C to Kawasaki Disease

A small portion of MIS-C patients allegedly match all KD criteria and that MIS-C and KD share a number of characteristics conditions such as aetiologies and pathophysiologies are unique or similar. Despite of the fact that many people first hypothesised that MIS-C was SARS-CoV-2-associated KD. It is now evident that the two syndromes appear to have significant variations, including patient age distributions, racial/ethnic bias clinical symptoms. The median age of MIS-C cases is 7–11 years, whereas KD affects kids under the age of five. Both MIS-C and KD affect men more frequently. Both diseases frequently begin with a fever that lasts longer than 38.0°C for five days, which is followed by a number of nebulous symptoms such nausea, diarrhoea, and abdominal pain. A rash, conjunctival injection, oropharyngeal erythema, and lip swelling or redness are also common symptoms in children with MIS-C, which are common symptoms in KD. Clinical aspects of MIS-C include substantially more extensive gastrointestinal, cardiac, and multi-organ involvement when compared to children with KD. The presence of cardiovascular involvement is also significantly more pronounced in MIS-C than in KD, including myocarditis, ventricular failure, and troponin increases. Additionally, the laboratory characteristics of MIS-C are different from those of KD and more similar to toxic shock syndrome. In contrast to KD patients, MIS-C patients have significantly greater procalcitonin and CRP levels and lower platelet and lymphocyte counts [8].

PATHOPHYSIOLOGY:

The pathophysiology remains incompletely understood. According to preliminary research, patients with severe MIS-C have persistent cytopenias (particularly T cell lymphopenia), persistent immunoglobulin G (IgG) antibodies that can more effectively activate CD8+ T cells and monocytes, which differ from findings in acute COVID-19 infection. Due to the small number of patients involved in these trials, the accuracy of

these findings is limited. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been theorised to be the cause of the syndrome, but it has a different immunopheno type from KD. The aberrant inflammatory response in MIS-C is most likely caused by host factors. End organ harm in MIS-C has been theorised to be caused by cytokine storm and endothelial dysfunction linked to SARS-CoV-2. Multiorgan failure and damage may be caused by this aberrant immune response. Cardiomyopathy, systemic inflammation, viral myocarditis, hypoxia, and/or coronary artery involvement leading to ischemia can all be factors in myocardial damage. According to autopsy results, cardiac tissue contained the SARS-CoV-2 virus as well as signs of pericarditis, myocarditis, and endocarditis with inflammatory cell infiltration.

Children who contract SARS-CoV-2 early on (Phase I) are likely to show no symptoms or only minor symptoms. While the pulmonary phase (phase II) is often minor or non-existent in youngsters, it is severe in adults. The first infection seems to activate macrophages and then stimulate T-helper cells. As a result, cytokines are released, macrophages, neutrophils, and monocytes are stimulated, B-cells and plasma cells are activated, and antibodies are produced, resulting in a hyperimmune response (stage III). In children that are affected, this immunological dysregulation is linked to the inflammatory syndrome. In MIS-C, ACE 2, TNF, BETA, and IL, direct infection with SARS-CoV-2 is less probable to be a factor [6].

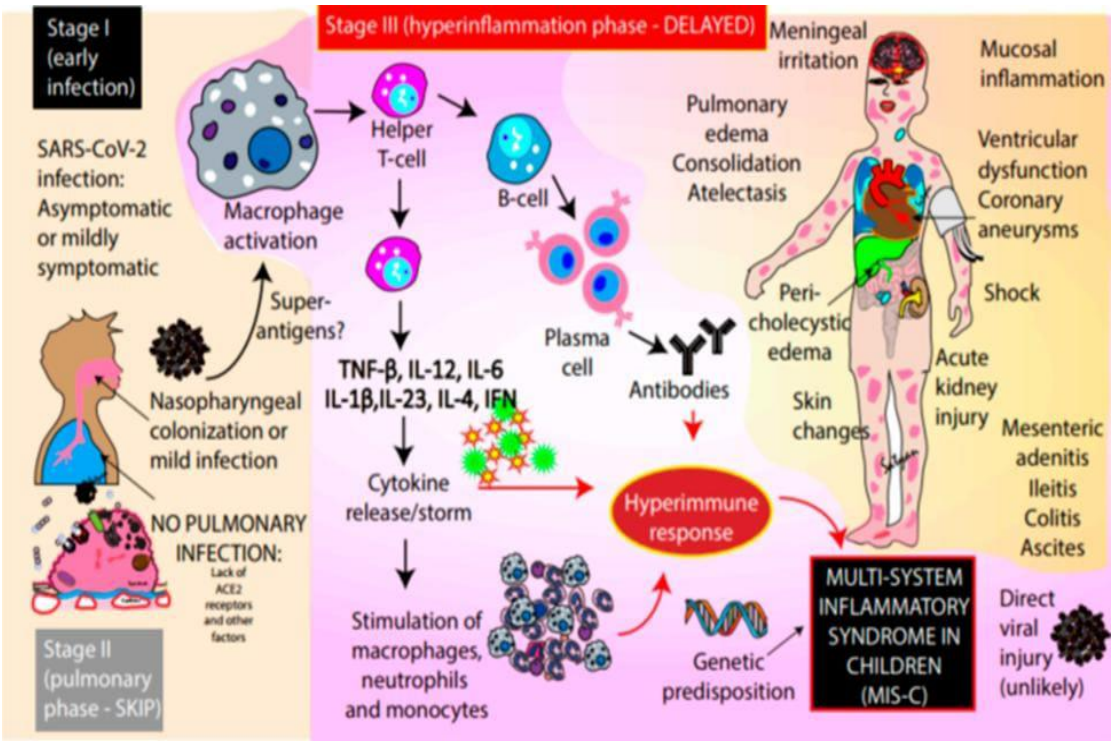

Figure 1: pathogenesis of MIS- C

SYMPTOMS OF MIS-C: [7]

After getting infected with the new coronavirus, symptoms of MIS-C often appear 2 to 5 weeks later. Children typically experience a mild course of COVID-19, which is frequently asymptomatic. Because of this, children can have COVID-19 but may be unaware that they have an infection. Children with MIS-C almost always have a temperature of at least 100.4°F for at least 24 hours. The fever often lasts between four and seven days. The clinical characteristic crieteria of MIS- C as per WHO includes that the child presents with fever ≥ 3 days, and the child should have atleast 2 of the following:

- Rash, conjunctivitis, mucocutaneous inflammation
- Hypotension or shock
- Cardiac involvement
- Coagulopathy
- Acute GI symptoms

Some patients may not have these features or some may have other features of organ invovements. GI symptoms (abdominal discomfort, vomiting, or diarrhoea), neurocognitive symptoms (headache, impaired mental status, or lethargy), respiratory symptoms (cough, sore throat), and myalgias are common in MIS-C patients. Myocardial

dysfunction, cardiogenic shock, multisystemic organ failure, and cytokine storm are possible presentations in severe cases, which can also include KD, septic shock, secondary hemophagocytic lymphohistiocytosis, and toxic shock syndrome presentations.

Diagnostic Testing:

Diagnosis complete based on the following criteria that whether the child really falls into the MIS-C case or not: [7]

- That is dose the child is having fever > 38°C,
- if any epidemiological link to SARS-COV- 2,
- Child is having atleast 2 suggestive clinical features.

If the child is yes to the above criertrias then the chid is consider to under investigation for further MIS-C. Therefore, a complete blood count (CBC), electrolytes, renal and liver function, elevated inflammatory markers (ESR and CRP), albumin, coagulation panel, D-dimer, SARS-CoV-2 testing (PCR and/or serologies), troponin, and brain natriuretic peptide (BNP) are all included in the diagnostic evaluation of a suspected MIS-C patient. 92% of patients have at least 4 of the following abnormalities, which include elevated ESR (> 40), elevated D-dimer, elevated CRP, lymphocytopenia, neutrophilia, elevated procalcitonin, elevated ferritin, hypoalbuminemia, anaemia, thrombocytopenia, or elevated liver enzymes. Elevated inflammatory markers are common. Common cardiovascular involvement symptoms include an increase in BNP/pro-BNP, troponin, and ECG. Repolarization abnormalities, ischemia changes, and first-degree atrioventricular block are the three most typical aberrant ECG findings. High-grade atrioventricular blocks, extended QT intervals, and bundle branch blocks are further observations. Pleural effusions, pulmonary consolidations, and radiographic signs of acute respiratory distress syndrome were further findings on chest radiography. Pericardial effusions, mitral or tricuspid regurgitation, and other cardiac conditions may be seen on an electrocardiogram or echocardiogram. Other investigation involves other system as well depending upon the system involvement. [8]

TREATMENT: [10, 11]

To date, there is no widely accepted guidelines for management of MIS-C. Children with MIS-C are treated in a hospital with multi-disciplinary approach in the care of the patient. A paediatric critical care unit is required for some patients. Supportive care is provided, and efforts are made to reduce inflammation in any affected organs to prevent long-term harm. The appropriate course of treatment depends on the type and degree of symptoms and also on the regions of organs that are inflamed.

Treatment is given by the following ways**:**

- Fluids, to treat dehydration as supportive care
- Hypotension is often treated with fluid resistant so add on inotropic such as vasopressors (epinephrine, noradrenaline).
- Oxygen for breathing assistance.
- Blood pressure medications to treat shock-related low blood pressure or to support heart function.
- If any evidence of severe myocardial dysfunction – Dobutamine is preferred.
- A ventilator, a breathing apparatus.
- Drugs that reduce the risk of blood clots, like heparin or aspirin.
- Antibiotics, Steroid therapy, Intravenous immunoglobulin (IVIG), an antibody-rich blood product, other forms of medicines intended to reduce high amounts of cytokine-producing proteins that can lead to inflammation.

The dosing regimens for the drugs recommended for the treatment of MIS-C:

Drug	**Dosing Regimens** (Fda-Approved recommendations)	**Adverse Events**	**Monitoring Parameters**
Intravenous Immunoglobulin	●IVIG 2 g/kg/BW dosage IV for 1 dose, with a 100 g maximum total dose. ●Consider administering IVIG in divided doses (1 g/kg IBW/dose IV every 24 hours for 2 doses) in cases of cardiac dysfunction or fluid overload.	● Hypersensitivity ● Fever ● Chills ● Flushing ● Hemolytic anemia	●Renal function ●Urine output ●CBC with differential ●Injection-related AE ●Anaphylaxis ●Signs and symptoms of hemolysis
Methylprednisolone – corticosteroids	●Every 12 hours, provide 1-2 mg/kg IV of methylprednisolone. ●Increase the dose to 10-30 mg/kg/day (up to a maximum of 1,000 mg/day) IV for 1-3 days if	● Adrenal suppression ● Hyperglycemia ● Sodium retention ● Fluid retention	●Blood pressure ●CBC with differential ●BMP

	the patient with MIS-C does not react to 1-2 mg/kg/dose IV every 12 hours.	● Leukocytosis ● Immune suppression	
Anakinra: treats MIS-C refractory or in patients who does not respond to the above treatent.	Anakinra 5–10 mg/kg/day IV or SC in 1 to 4 divided doses. It is an interleikin 1 receptor blocker.	● Headache ● Fever ● Hypersensitivity ● Immune suppression ● Transaminitis	●CBC with differential ●LFTs ●Scr
Infliximab	5-10 mg/kg/dose IV of infliximab given once	● Infusion-related reaction ● Headache ● Immune suppression	●During the infusion, check the vital signs every 2 to 10 minutes. ●CBC with differential
Aspirin: given to individuals with thrombocytopenia, MIS-C, and KD-like characteristics.	3–5 mg/kg aspirin per dose, up to a maximum of 81 mg per dose PO once per day	● Gastrointestinal ulcers ● Hypersensitivity ● Renal dysfunction	●bleeding symptoms or signs ●Renal function
Enoxaparin: given in patients with documented thrombosis or an EF of <35%. And given to the patient with on going moderate to severe LV dysfunction.	●Ages >2 months to >18 years: 0.5 mg/kg/dose (up to a maximum of 30 mg/dose) of enoxaparin every 12 hours SUBQ ●Ages >2 months to >18 years: Enoxaparin Treatment, 1 mg/kg/dose SUBQ every 12 hours ●Keep track of antifactor Xa activity (therapeutic range: 0.5 to 1).	● higher chance of bleeding ● Thrombocytopenia	●CBC with differential ●Renal function

Conclusion:

A novel hyperinflammatory condition with severe multisystem involvement has been described in children and adolescents during the COVID-19 pandemic (PIMS-TS/MIS (-C)). Further epidemiological, clinical, immunological, and genetic research is needed, as well as long-term follow-up studies of PIMS-TS/MIS (-C) patients. With severe symptoms and a high index of suspicion for MIS-C following COVID, this condition can impact almost any organ system. Symptoms of MIS-C include fever, gastrointestinal discomfort, neurological symptoms, and dermatological changes. Treatment for MIS-C is customised to address particular systemic symptoms or results. Emerically treat for common infectionas wll if not test for COVID.

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