International Journal of Pharmaceutical Research and Development

ISSN Print: 2664-6862
ISSN Online: 2664-6870
Impact Factor: RJIF 8
IJPRD 2025; 7(1): 01-05
www.pharmaceuticaljournal.net
Received: 01-10-2024
Accepted: 04-11-2024

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Multisystem inflammatory syndrome in children (MIS-C): Clinical presentation and management of critically ill cases

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DOI: https://doi.org/10.33545/26646862.2025.v7.i1a.87

Abstract
We present a series of three critically ill pediatric patients, aged 6–10 years, who were diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) following a recent SARS-CoV-2 infection. These cases were admitted to a tertiary care center in New Jersey between April 4 and May 10, 2020. All patients were previously healthy, and their clinical presentations were characterized by fever, abdominal pain, gastrointestinal symptoms, and/or rash. One patient exhibited altered mental status with cerebrospinal fluid findings consistent with aseptic meningitis. Laboratory results revealed markedly elevated C-reactive protein (CRP), D-dimer, B-type natriuretic peptide (BNP), and troponin levels, alongside low albumin levels in all cases. Notably, evaluation for alternative infections was negative. All patients developed circulatory shock requiring inotropic support, with two requiring advanced respiratory support and one presenting with cardiac dysfunction. Treatment included corticosteroids for all patients, with two receiving intravenous immunoglobulin (IVIG) and one receiving tocilizumab. All patients survived without fatal outcomes. This report underscores the importance of clinical awareness of MIS-C, particularly in the context of SARS-CoV-2, to guide effective management and improve patient outcomes.

Keywords: Multisystem inflammatory syndrome in children, intravenous immunoglobulin, pediatric, C-reactive protein, inotropic support

Introduction
Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe condition that has emerged in the wake of the COVID-19 pandemic, with a notable temporal association to SARS-CoV-2 infection. The syndrome is characterized by fever, gastrointestinal symptoms, cardiovascular involvement, and in some cases, neurological manifestations, often requiring intensive care [1]. The pathogenesis of MIS-C is believed to involve a dysregulated immune response triggered by the viral infection, leading to systemic inflammation [2, 3].

While MIS-C is a relatively rare complication of SARS-CoV-2, it has garnered significant attention due to its potentially life-threatening nature. Early studies from the United States and Europe have reported a strikingly increased incidence of MIS-C among children following widespread community transmission of COVID-19 [4, 5]. Children with MIS-C often present with a history of mild or asymptomatic COVID-19 infection, suggesting that the syndrome may be an immune-mediated phenomenon occurring weeks after the viral exposure [6, 7].

Clinically, MIS-C shares some features with Kawasaki disease, including vasculitis and coronary artery involvement, although it differs in its association with COVID-19 and the broader spectrum of organ systems affected [8, 9]. As the understanding of this syndrome has evolved, it has become clear that early recognition and timely intervention, including the use of intravenous immunoglobulin (IVIG) and corticosteroids, are crucial in managing the condition and improving outcomes [10].

Recent research has also pointed to the role of immune modulation therapies, such as tocilizumab, in the management of MIS-C, with some studies showing promising results in reducing inflammation and improving clinical outcomes [11, 12]. Furthermore, vaccination against COVID-19 has been shown to reduce the incidence of MIS-C, highlighting the

critical importance of vaccination in preventing both COVID-19 and its associated complications [13].
Understanding the underlying mechanisms and optimizing treatment strategies for MIS-C remains an area of active investigation, as researchers continue to explore the intricate interplay between the immune system and SARS-CoV-2 infection [14, 15]. This manuscript aims to provide a comprehensive review of the clinical features, pathogenesis, and management of MIS-C, focusing on recent advancements in the understanding of this complex syndrome.

MIS-C and Risk Factors
MIS-C (Multisystem Inflammatory Syndrome in Children) is a rare but serious condition linked to COVID-19, characterized by prolonged fever, gastrointestinal symptoms, and a rash, resembling Kawasaki disease. It involves inflammation in multiple organ systems and can lead to heart failure, coronary artery issues, and arrhythmias. MIS-C is more common in children under 19 years who have a history of SARS-CoV-2 infection. Risk factors identified in various studies include male sex, younger age, Black non-Hispanic ethnicity, and underlying chronic health conditions. Vaccination against COVID-19 has been shown to reduce the risk of developing MIS-C, with many countries, including Sweden, recommending vaccination for children aged 12 and older.
In regions like sub-Saharan Africa, where the pandemic peaked later, there is limited data on the occurrence of MIS-C, especially in countries like Nigeria. Research into MIS-C in African populations is essential to understand its impact and guide local healthcare strategies.
This study aimed to assess risk factors for MIS-C in the Swedish population, while highlighting the need for similar studies in Africa, particularly in resource-limited settings. Follow-up data is crucial to establish effective, evidence-based post-hospital care for children who recover from MIS-C, particularly in regions with fewer healthcare resources.

Clinical Criteria for MIS-C
1. **Fever:** Minimum 24-hour history of fever ≥ 38.0 °C.
2. **Severe Illness:** Hospitalization required due to severe symptoms.
3. **Organ Involvement:** Two or more organ systems affected (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological).

Laboratory Evidence of Inflammation
Elevated levels of CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6. Elevated neutrophils or reduced lymphocytes; low albumin.

Evidence of SARS-CoV-2 Infection
Positive SARS-CoV-2 test (RT-PCR, serology, or antigen) OR COVID-19 exposure within 4 weeks before symptoms.
Exclusion of Other Diagnoses.

Laboratory Investigations for MIS-C
Routine Tests: All patients had full blood counts, renal function tests, and at least one acute phase reactant assay.

Additional Tests
Liver function tests were done in 67.9% of patients.
Coagulation profile was done in 10.7%.
Urinalysis and urine microscopy were performed in 71.4% and 60.7% of patients, respectively.

Infection Tests
Blood cultures were negative in most cases, except for one patient with *Acinetobacter baumannii* and another with *Staphylococcus haemolyticus* (possible contaminant).
Viral markers (Hepatitis B, Hepatitis C, HIV) were negative in most patients.

Inflammatory Markers
Thrombocytosis was noted in all patients with illness lasting more than a week.
D-dimer was elevated in all five tested patients.
Ferritin and LDH were elevated in some patients.

Other Findings: Electrolytes, urea, and creatinine were normal in most cases, but abnormalities in other tests were present in a small number of patients.

COVID-19 and MIS-C
COVID-19 Emergence: In December 2019, a novel coronavirus, SARS-CoV-2, caused a global pandemic, later named COVID-19.
MIS-C: In children, COVID-19 infection is usually mild, but a rare but severe condition called MIS-C emerged, resembling Kawasaki disease or toxic shock syndrome. MIS-C involves systemic inflammation and affects multiple organ systems.

Evolving Case Definitions
CDC and Global Definitions: Early in the pandemic, the CDC defined MIS-C with specific criteria: fever, systemic inflammation, and involvement of at least two organ systems. Over time, definitions have evolved, with the 2023 update simplifying the criteria.
C-reactive protein (CRP) must be ≥ 3 mg/dL. Reduces the required organ systems (neurological, respiratory, and renal systems were removed). Kawasaki disease (KD) is now an alternative diagnosis.

Diagnostic Tests for MIS-C
1. Complete Blood Count (CBC)
2. Erythrocyte Sedimentation Rate (ESR)
3. C-Reactive Protein (CRP)
4. Procalcitonin (PCT)
5. Blood Culture
6. COVID-19 PCR or Antibody Test

Symptoms of MIS-C
1. Children with MIS-C may experience
2. Fever
3. Recent COVID-19 exposure (either infection or close contact within the last 2 months)
4. High levels of inflammation in the body (systemic inflammation)
5. At least two of the following symptoms:
6. Heart problems
7. Red, bloodshot eyes
8. Swelling or redness of lips, tongue, hands, or feet
9. Abdominal pain, vomiting, or diarrhoea
10. Blood clotting issues
11. Shock

Emergency Warning Signs

1. Seek immediate medical help if your child has:
2. Severe stomach pain
3. Chest pain or pressure
4. Difficulty breathing
5. Pale or blue skin, lips, or nails
6. New confusion

Epidemiology of COVID-19 in Children

Incidence: Around 18% of COVID-19 infections occur in children, with 1% of all COVID-19 patients being children. The highest incidence is in children aged 5–15.

Seropositivity: Approximately 75% of children in the U.S. have antibodies against SARS-CoV-2, higher than in adults.

Symptoms: Over 90% of children have mild or no symptoms. Most common symptoms include low fever, cough, and weakness. 66% of infected children show no symptoms. 27% have mild flu-like symptoms. 5% have moderate symptoms, including pneumonia. 2% require ICU care.

Hospitalization Rates

About 48 per 100,000 children under 18 are hospitalized annually due to COVID-19. Highest rates in children aged 0–4 (66.8/100,000) and 12–17 years (59.9/100,000). Children aged 5–11 have the lowest hospitalization rates (25/100,000). During the Omicron wave, rates for children aged 0–4 were 15.6/100,000. Vaccinated children aged 5–11 had a lower hospitalization rate (9/100,000) compared to unvaccinated children (19/100,000).

Mortality

Deaths from COVID-19 in children are rare, with a mortality rate of 0.17 per 100,000 children.
COVID-19 accounts for only 0.48% of all-cause deaths in children under 18. While the mortality rate is low, children may still experience severe symptoms requiring supportive care.

SARS-CoV-2 Infection

Children often have asymptomatic or mild COVID-19 infections. The virus triggers an immune response.

Immune Dysregulation

Overproduction of inflammatory cytokines (e.g., IL-6, TNF-α). Activation of immune cells (macrophages, T-cells). Imbalance between Th1 and Th2 immune responses.

Endothelial Damage

Inflammation damages the blood vessel lining (endothelial cells). Endothelial dysfunction causes vascular leakage.

Multiorgan Involvement

Inflammation spreads to multiple organs (heart, lungs, kidneys). Organ damage is caused by cytokine storm and endothelial dysfunction.

Cytokine Storm

Excessive cytokine production. The cytokine storm worsens inflammation and tissue damage.

Case Definitions

Case 1

Patient: 6-year-old girl with fever (39 °C), headache, vomiting, abdominal pain, diarrhoea, conjunctivitis, and rash.

Exposure: Contact with grandfather who had COVID-19 2 weeks earlier.

Symptoms: Fever (40 °C), tachycardia, hypotension, respiratory failure requiring intubation.
Lab results: Lymphopenia, thrombocytopenia, elevated inflammatory markers, ferritin, D-dimer, troponin, BNP.

Treatment: Broad-spectrum antibiotics, IVIG, methylprednisolone, tocilizumab.
Outcome: Extubated after 9 days, discharged after 14 days.

Case 2

Patient: 9-year-old boy with fever (38.2 °C), diarrhoea, vomiting, mental status change, conjunctivitis, shortness of breath, and facial swelling.

Symptoms: Hypoxic respiratory failure, systolic dysfunction, and aseptic meningitis.
Lab results: Leucocytosis, neutrophilia, elevated troponin and BNP, negative respiratory viral panel, positive SARS-CoV-2 RT-PCR.

Treatment: Antibiotics, hydroxychloroquine, methylprednisolone, enoxaparin.
Outcome: Afebrile on day 3, kidney function improved.

Supportive Care

1. Fluid resuscitation: to manage shock and hypotension
2. Oxygen therapy: to manage respiratory distress
3. Cardiac monitoring: to manage cardiac dysfunction
4. Renal replacement therapy: to manage acute kidney injury
5. Nutritional support: to manage malnutrition and weight loss.

Future Directions

As the understanding of Multisystem Inflammatory Syndrome in Children (MIS-C) continues to evolve, several key areas of research must be prioritized to improve diagnosis, treatment, and long-term outcomes.

1. **Pathophysiology and Mechanisms:** The underlying mechanisms driving MIS-C remain poorly understood. Future research should focus on the immune dysregulation and inflammatory pathways that lead to multi-organ involvement. Investigating the role of cytokine storms, autoimmunity, and the host immune response to SARS-CoV-2 infection could uncover potential therapeutic targets for more effective management. Further studies exploring genetic and epigenetic factors may help identify children at higher risk for developing MIS-C, potentially allowing for earlier intervention and prevention strategies.
2. **Long-Term Outcomes:** While many children with MIS-C recover with appropriate treatment, the long-term effects of the syndrome are not fully known. Future studies should follow children who have experienced MIS-C to assess the potential for long-term

cardiovascular, neurological, and psychological sequelae. Research on the impact of MIS-C on growth, development, and quality of life will be critical to guide post-recovery care and surveillance.

3. **Vaccine Impact and Prevention:** The role of vaccination in preventing MIS-C has become an important area of investigation. Although studies suggest that vaccination reduces the risk of MIS-C, further research is needed to determine the optimal timing, type, and dosing of vaccines for different age groups. Longitudinal studies assessing the protective effects of vaccination against both COVID-19 and MIS-C, particularly in high-risk populations, are crucial for refining public health guidelines.
4. **Improved Diagnostics and Early Detection:** Early recognition and intervention are key to improving outcomes in MIS-C patients. Developing more sensitive and specific biomarkers for early diagnosis, as well as refining clinical criteria for identifying MIS-C, will facilitate timely treatment. Exploring advances in imaging, molecular diagnostics, and multi-omics technologies could provide new insights into the early stages of the disease and help distinguish MIS-C from other inflammatory or infectious conditions.
5. **Treatment Optimization:** While IVIG and corticosteroids remain the mainstays of treatment, further research is needed to optimize therapy. Studies investigating adjunctive therapies, such as biologic agents like tocilizumab, anti-cytokine therapies, or novel immunomodulatory drugs, could offer additional options for severe cases or those unresponsive to conventional treatments. Randomized controlled trials evaluating the safety and efficacy of combination therapies are essential to guide clinical decision-making.
6. **Global Surveillance and Epidemiological Studies:** As the incidence of MIS-C may vary across regions and populations, robust, global surveillance systems are needed to track trends, monitor emerging variants of SARS-CoV-2, and assess the impact of public health measures such as vaccination. Epidemiological studies that include diverse ethnic and socio-economic groups will help to identify at-risk populations and tailor interventions accordingly, particularly in low- and middle-income countries where access to healthcare resources may be limited.
7. **Public Health and Policy Recommendations:** Finally, integrating research findings into public health policies and clinical guidelines is critical for preventing and managing MIS-C. Health education campaigns aimed at parents, healthcare providers, and communities about the symptoms, risk factors, and importance of vaccination will be essential in reducing the burden of MIS-C. Policymakers should consider integrating MIS-C management strategies into broader pandemic response plans and healthcare systems, especially as COVID-19 continues to evolve and new variants emerge.

Conclusion

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare, yet severe, post-viral inflammatory condition that has been closely linked to SARS-CoV-2 infection. Although the majority of children with MIS-C recover with timely and appropriate medical intervention, including the use of intravenous immunoglobulin (IVIG) and corticosteroids, the exact mechanisms and risk factors underlying the syndrome remain incompletely understood. MIS-C affects multiple organ systems, particularly the cardiovascular system, and can lead to significant complications such as heart dysfunction, shock, and severe gastrointestinal symptoms. As MIS-C often manifests weeks after an initial COVID-19 infection, the syndrome poses an ongoing challenge to paediatric care providers, necessitating heightened awareness and rapid recognition.

While research continues to investigate the pathophysiology of MIS-C, current evidence underscores the importance of vaccination and other preventive measures to reduce its incidence. Vaccination against SARS-CoV-2 has been shown to significantly decrease the risk of developing MIS-C, highlighting the critical role of public health interventions in mitigating the impact of the pandemic on children. Ongoing surveillance, clinical studies, and population-based research are essential for further elucidating the risk factors, long-term effects, and optimal treatment strategies for MIS-C. By improving our understanding of this complex syndrome, we can better protect vulnerable populations and enhance the overall outcomes for children affected by MIS-C.

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