



Pharmacological Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

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Clinical Drug Information | Clinical Solutions

Highlights:

- Multisystem inflammatory syndrome in children (MIS-C) is a rare, but severe inflammatory syndrome that has been reported in pediatric patients post SARS-CoV-2 exposure. There are similarities between MIS-C and atypical Kawasaki disease; however, some clinical differences have been noted, such as older age at presentation, a higher incidence of gastrointestinal symptoms on presentation, and a higher rate of cardiac involvement. (1) (2) (3) (24)
- Management focuses on supportive care and treatment of the underlying inflammatory process in an effort to reverse organ dysfunction and prevent further complications. Although there are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for this indication, several agents are being used in clinical trials and institutional protocols based on their clinical benefit in similar conditions and limited experience in the management of MIS-C. (3) (24)
- Excellent supportive care is essential for all cases. Pharmacologic therapy must be tailored to the individual child and specific presentation. Aggressive management may be necessary for patients with severe disease, particularly those with myocarditis and those who meet the criteria for Kawasaki disease or toxic shock. (2) (4)
- **Pharmacological therapies used for MIS-C:**
 - Intravenous Immunoglobulin (IVIG) – Anti-inflammatory/immunomodulatory actions have resulted in a reduction of coronary artery abnormalities in patients with Kawasaki disease; successfully used for MIS-C in multiple published reports and institutional protocols.
 - Aspirin – Reduces coronary artery abnormalities in Kawasaki disease; used in some published reports and institutional protocols. Consider for patients who meet Kawasaki disease criteria.
 - Corticosteroids – Included in most published reports and institutional protocols, especially in patients with IVIG resistance.
 - Immunomodulating Agents [Interleukin Receptor Antagonists] – Used in limited protocols based on theoretical mechanisms.

- **Adjunctive / supportive care**

- Anticoagulation – Used in some published reports; the risk of venous thromboembolism (VTE) in MIS-C patients is unknown.
- Hemodynamic Support – Fluid resuscitation and vasopressor/inotrope support may be necessary for patients who develop hemodynamic instability.

Pharmacological therapy:

- Careful supportive care may be appropriate for some patients with mild symptoms; however, patients must be closely monitored due to the risk for rapid and severe decompensation. (4) (32)
- Empiric antibiotic therapy is recommended until bacterial infection has been ruled out. (32)
- Clinical guidance recommends a stepwise progression of immunomodulatory therapy, with IVIG and/or corticosteroids being the first tier. (27)
- Fluid status must be evaluated prior to IVIG administration. IVIG products are delivered in large volumes, which can significantly contribute to daily fluid balance, particularly in children. An adjustment in other fluid intake may be necessary.

Intravenous Immunoglobulin (IVIG):

- Classification: Human immunoglobulin G (IgG) with trace amounts of IgA and IgM
- Rationale for Use: Produces generalized anti-inflammatory effects; reduces coronary artery abnormalities in patients with Kawasaki disease. Positive response has been seen in patients with MIS-C. (3) (4) (5)
- Mechanism of Action: The precise mechanism of action in the management of MIS-C is undefined; it appears to have generalized anti-inflammatory effects. Immunoglobulins are antibodies synthesized by B lymphocytes. IVIG is derived from the pooled human plasma of thousands of donors. Most preparations consist of intact IgG molecules with trace amounts of IgA, IgM, soluble CD4, CD8, human leukocyte antigen (HLA), and cytokines. The pooled, heterogenous IgG present in IVIG provides a plethora of antibodies capable of opsonization and neutralization of many toxins and microbes as well as complement activation. The Fc fragment of the IgG molecule allows the molecule to interact with and signal through Fc- gamma receptors on B cells and other cells of the phagocytic system. The Fc fragment also interacts with the Fc-binding plasma proteins, which is essential for complement activation and microorganism clearance. In immunomodulatory and anti-inflammatory disease states, it is believed the Fc fragment of IgG and the Fc-gamma receptors on target cells (e.g., macrophages, B cells, natural killer cells, plasma cells, eosinophils, neutrophils, platelets) interact to up-regulate or down-regulate inflammatory and immune responses.(6)
- Evidence / Experience:
 - Appears to be evolving as standard of care for severe cases.
 - 1,000 to 2,000 mg/kg IV as a single dose in combination with aspirin and/or methylprednisolone has been reported and is being used in some institutional protocols. Depending on the severity of illness, additional doses have been administered. Cardiac function and fluid status influence the timing of therapy. (1) (4) (7) (8) (27) (28) (31) (33)
 - American College of Rheumatology draft guidance recommendation (27):
 - IVIG 1,000 to 2,000 mg/kg and/or steroids as first line treatment.

- Assessment of cardiac function and fluid status in MIS-C patients with shock is recommended before IVIG treatment; administer IVIG once cardiac function is restored.
 - In 1 review, authors suggest IVIG 2,000 mg/kg typically given as a single dose for patients meeting Kawasaki disease criteria and 1,000 to 2,000 mg/kg for patients meeting secondary hemophagocytic lymphohistiocytosis (SHLH) criteria. (30)
 - Clinical characteristics of 186 pediatric patients meeting criteria for MIS-C were reported. Seventy-seven percent of patients received IVIG on the sixth median day of illness; a second dose was administered in 21% of patients. Eighty percent of patients were in the intensive care unit and 20% received mechanical ventilation. As of study end, 70% of patients were discharged alive, 28% were still hospitalized, and 2% had died. (28)
 - In another report, clinical characteristics of 99 patients with confirmed MIS-C were described. Seventy percent of patients received IVIG and 48% of patients received IVIG and steroids. At study end, 77% of patients had been discharged, 21% were still hospitalized, and 2% had died. The median length of stay was 6 days overall, 6 days among patients who were discharged, and 7 days among those who died. Neither patient that died received IVIG, steroids, or immunomodulators. (29)
 - In a prospective observational study (n = 21, age 3 to 16 years), patients received IVIG after fever for a median duration of 5 days (range 0 to 12 days); 5 patients received a second dose due to IVIG resistance. Seventeen patients were admitted to an intensive care unit (ICU) for hemodynamic instability. The median ICU length of stay was 5 days (range 3 to 15 days). All patients were discharged home after a median hospital stay of 8 days (range 5 to 17 days). (7)
 - In a retrospective study (n = 16, median age 10 years), 15 patients received IVIG; 4 patients received an additional IVIG dose, and 1 received a second IVIG infusion with steroids. The median time between initiated treatments and clinical remission was 2 days (range 1 to 8 days). (25)
 - In a retrospective study (n = 15, median age 8.8 years), IVIG was administered to 10 patients. Two patients with persistent fever and/or worsening inflammatory markers after 36 hours received a second IVIG infusion. All patients were discharged home after a median hospital stay of 12 days (range 9 to 13 days). (26)
 - In a retrospective study (n = 10, age 2 to 16 years), all patients responded to acute treatment after a single dose of IVIG. (1)
 - In a case series (n = 6, age 5 to 14 years), 1 dose of IVIG was administered to all patients, and 2 patients received a second dose due to ongoing fevers. Five of the 6 patients had resolution of fever and improvement in cardiac function over a period of days. (8)
 - In a retrospective study (n = 35, age 2 to 16 years), 25 patients received IVIG (dose not specified) with 1 patient receiving a repeat dose due to persistent fever. Thirty-four patients were discharged after a median hospital stay of 8 days; 5 patients had residual mild to moderate left ventricular systolic dysfunction at last follow-up. (2)
- Safety Concerns: (9) (10) (11)
 - Caution in patients with delicate fluid balance; daily fluid intake may need adjustment
 - Caution in patients at risk of thromboembolism
 - Patients at greatest risk are those with cardiovascular risk factors, coagulation disorders, prolonged periods of immobilization, a history of a previous thromboembolic event, use of estrogens, indwelling catheters, and/or known or suspected hyperviscosity.

- Caution in patients with renal impairment
 - More common with IVIG products containing sucrose as a stabilizer.

Aspirin:

- Classification: Antithrombotic therapy
- Rationale for Use: Has anti-inflammatory properties and antiplatelet activity; consider in patients who meet Kawasaki disease criteria. (3) (4) (5) (27) (33)
- Mechanism of Action: The anti-inflammatory action of aspirin is believed to be a result of peripheral inhibition of COX-1 and COX-2, but aspirin may also inhibit the action and synthesis of other mediators of inflammation. The antithrombotic actions of aspirin are primarily mediated by COX-1 inhibition; COX-1 produces thromboxane A₂ (TXA₂). TXA₂ is a potent vasoconstrictor and platelet agonist. Aspirin may also inhibit platelet activation by neutrophils. (12) (13) (14) (15)
- Evidence / Experience:
 - Doses varying from 3 to 5 mg/kg/day orally (low dose) to 30 to 100 mg/kg/day orally (moderate to high dose) have been reported and are being used in some institutional protocols in combination with IVIG with or without methylprednisolone. (1) (4) (7) (8) (31) Although ranges are provided in clinical studies, the optimal duration of treatment or recommendations on dividing larger doses is not always described. However, when treating other conditions, high doses of aspirin are divided into 2 to 4 doses.
 - At a minimum, low dose aspirin is recommended for patients with Kawasaki disease-like syndrome. (33)
 - American College of Rheumatology draft guidance recommendation (27):
 - Low dose aspirin (3 to 5 mg/kg/day; max 81 mg/day) in patients with MIS-C and Kawasaki disease-like features and/or thrombocytosis (platelet count 450,000/microliter or more).
 - Continuation is recommended until platelet count and coronary arteries are normal for at least 4 weeks after diagnosis. Avoid treatment in patients with a platelet count of 80,000/microliter or less.
 - Additionally, it is recommended that patients with coronary artery aneurysms and a maximal z-score of 2.5 to 10 be treated with low dose aspirin, whereas, patients with a z-score of 10 or more be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin.
 - In 1 institutional protocol, aspirin 20 to 25 mg/kg/dose every 6 hours (80 to 100 mg/kg/day) is recommended in patients with Kawasaki disease-like illness, evidence of excessive inflammation (ferritin more than 700 ng/mL, CRP more than 300 g/dL, or multisystem organ failure), or cardiac involvement. Once patients are afebrile for 24 hours or more, the aspirin dose is reduced to 3 to 5 mg/kg/day. (4)
 - In 1 review, authors suggest aspirin 30 to 50 mg/kg/day, decreasing to 3 to 5 mg/kg/day once patients are afebrile for 48 hours in patients meeting Kawasaki disease criteria. (30)
 - In a prospective observational study (n = 21, age 3 to 16 years), all patients received low dose aspirin 3 to 5 mg/kg/day in combination with IVIG. Seventeen patients were admitted to an intensive care unit (ICU) for hemodynamic instability. The median ICU length of stay was 5 days (range 3 to 15 days). All patients were discharged home after a median hospital stay of 8 days (range 5 to 17 days). (7)

- In a retrospective study (n = 16, median age 10 years), 7 patients received aspirin 30 to 80 mg/kg/day and 8 patients received antiplatelet doses. All patients were discharged home on antiplatelet aspirin therapy. (25)
- In a retrospective study (n = 15, median age 8.8 years), aspirin 12.5 mg/kg/dose 4 times a day was administered to 2 patients; 11 patients were discharged on low dose aspirin. All patients were discharged home after a median hospital stay of 12 days (range 9 to 13 days). (26)
- In a retrospective study (n = 10, age 2 to 16 years), aspirin 50 to 80 mg/kg/day or aspirin 30 mg/kg/day plus methylprednisolone, depending on the risk of IVIG resistance, was given for 5 days in combination with IVIG. Aspirin was continued until 48 hours after defervescence and then continued at 3 to 5 mg/kg/day for 8 weeks. All patients responded to acute treatment. (1)
- In a case series (n = 6, age 5 to 14 years), low dose aspirin was administered to 3 patients in combination with IVIG. Five of the 6 patients had resolution of fever and improvement in cardiac function over a period of days. (8)
- Long-term cardiac follow-up is currently unavailable; echocardiogram data on coronary artery aneurysms are pending. (16)
- **Safety Concerns:** (14) (21) (22) (23)
 - Monitor for elevated liver function tests (LFTs)
 - Patients receiving large doses of aspirin or patients with preexisting hepatic impairment are at increased risk.
 - Caution in patients with renal impairment
 - Caution in patients at risk for bleeding

Corticosteroids:

- **Classification:** Systemic hormonal agent
- **Rationale for Use:** Has anti-inflammatory properties. (3) (4) Most patients respond well to intravenous immunoglobulin (IVIG), but about 10% to 20% require additional anti-inflammatory treatment. (16)
- **Mechanism of Action:** Glucocorticoids prevent or suppress inflammation and immune responses when administered at pharmacological doses. At the molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately, protein synthesis to achieve the steroid's intended action. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, collectively called lipocortins. Lipocortins, in turn, control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the precursor molecule arachidonic acid. (17) (18)
- **Evidence / Experience:**
 - 2 to 30 mg/kg/day IV has been reported, depending on the severity of illness, and is being used in combination with IVIG with or without aspirin. A 3-week at-home taper has been recommended. (1) (4) (7) (8) (33)
 - American College of Rheumatology draft guidance recommendation (27):
 - Consideration of low to moderate dose steroids.
 - High dose, IV pulse steroids may be considered to treat patients with life-threatening complications, such as shock, or if a patient requires high dose or multiple inotropes and/or vasopressors.

- In 1 institutional protocol, methylprednisolone 3-day pulse dosing is recommended in high-risk patients (infants, Kawasaki disease shock syndrome, CRP more than 130 g/dL, admission echo Z score more than 2.5 or aneurysms, or Asian race) in combination with IVIG. (4)
- In another institutional protocol, prednisone, prednisolone, or methylprednisolone are recommended in high-risk patients with Kawasaki disease features. For patients with a mild presentation (defined as requiring minimal to no respiratory support, no vasoactive requirements, minimal to no organ injury, and does not require ICU admission), 2 mg/kg/day divided every 8 to 12 hours is recommended. For patients with a severe presentation (defined as significant oxygen requirement, mild to severe organ injury and/or ventricular dysfunction, vasoactive requirement, or ICU admission), pulse dosing with 10 to 30 mg/kg/day for 1 to 3 days then decreased to 2 mg/kg/day divided every 8 to 12 hours followed by a steroid taper is recommended. (31)
- In 1 review, authors suggest 2 dosing strategies for patients with symptoms of severe Kawasaki disease (KD), defined by fever or persistent inflammation for 48 hours or more after IVIG, Kobayashi score of 5 or more, features of secondary hemophagocytic lymphohistiocytosis (SHLH), shock, age younger than 1 year, or coronary or peripheral aneurysms at the time of diagnosis, and 1 dosing strategy for patients with signs and symptoms of SHLH. (30)
 - Dosing strategy 1 for severe KD: Methylprednisolone 0.8 mg/kg/dose IV twice daily for 5 to 7 days or until CRP normalizes followed by oral prednisone/prednisolone 2 mg/kg/day tapered over 2 to 3 weeks.
 - Dosing strategy 2 for severe KD: Methylprednisolone 10 to 30 mg/kg/dose IV daily for 3 days followed by oral prednisone/prednisolone 2 mg/kg/day until day 7 or until CRP normalizes and then tapered over 2 to 3 weeks.
 - Dosing strategy for SHLH: Methylprednisolone 30 mg/kg/dose IV daily for 3 doses followed by 1 mg/kg/dose IV every 12 hours. Pediatric rheumatology, immunology, or hematology-oncology consult recommended to aid in tapering.
- Clinical characteristics of 186 pediatric patients meeting criteria for MIS-C have been reported. Forty-nine percent of patients received steroids in addition to IVIG. Eighty percent of patients were in the intensive care unit and 20% received mechanical ventilation. As of study end, 70% of patients were discharged alive, 28% were still hospitalized, and 2% had died. (28)
- In another report, clinical characteristics of 99 patients with confirmed MIS-C were described. Sixty-four percent of patients received steroids and 48% of patients received IVIG and steroids. At study end, 77% of patients had been discharged, 21% were still hospitalized, and 2% had died. The median length of stay was 6 days overall, 6 days among patients who were discharged, and 7 days among those who died. Neither patient that died received IVIG, steroids, or immunomodulators. (29)
- In a prospective observational study (n = 21, age 3 to 16 years), 7 patients received corticosteroids 2 to 10 mg/kg/day. Seventeen patients were admitted to an intensive care unit (ICU) for hemodynamic instability. The median ICU length of stay was 5 days (range 3 to 15 days). All patients were discharged home after a median hospital stay of 8 days (range 5 to 17 days). (7)
- In a retrospective study (n = 10, age 2 to 16 years), 8 patients received methylprednisolone 2 mg/kg/day plus aspirin for 5 days, followed by tapering of methylprednisolone over 2 weeks. All patients responded to treatment. (1)

- In a case series (n = 6, age 5 to 14 years), methylprednisolone 2 to 10 mg/kg/day was given to all patients. Two patients with either a lack of response or a worsening condition received methylprednisolone 30 mg/kg/dose. Five of the 6 patients had resolution of fever and improvement in cardiac function over a period of days. (8)
- In a retrospective study (n = 35, age 2 to 16 years), 12 patients who were considered high risk received IV corticosteroids (dose not specified). Thirty-four patients were discharged after a median hospital stay of 8 days; 5 patients had residual mild to moderate left ventricular systolic dysfunction at last follow-up. (2)
- Safety Concerns: (19)
 - Caution in patients with diabetes mellitus
 - Caution in patients with immunosuppression

Interleukin-1 (IL-1) Antagonists:

- Rationale for Use: Cytokine release syndrome may contribute to severe inflammation in some patients with MIS-C. (4)
- Mechanism of Action: Interleukin-1 antagonists prevent the binding of IL-1 (a pro-inflammatory cytokine that mediates various inflammatory and immunological responses) to interleukin-1 receptors. Anakinra acts similarly to the native interleukin-1 receptor antagonist by competitively inhibiting the binding of both IL-1 alpha and IL-1 beta to the IL-1 type 1 receptor. (19)
- Evidence / Experience:
 - 2 to 10 mg/kg/day subcutaneously or IV divided every 6 to 12 hours has been recommended with a 3-week at-home taper. (30) (33)
 - American College of Rheumatology draft guidance recommendation (27):
 - Consideration of anakinra for treatment refractory to IVIG and steroids or in patients with contraindications to these treatments.
 - In 1 institutional protocol, use is recommended in patients with severe inflammation consistent with cytokine storm syndrome if patients are not responding to first-line therapies.(4)
 - In another institutional protocol, anakinra may be considered if fever continues for more than 24 hours after steroids and IVIG or presentation is defined as moderate to severe. For patients with moderate presentation, 2 mg/kg/dose subcutaneously once daily (Max: 100 mg/dose) is recommended for 5 days. In patients with a severe presentation (defined as significant oxygen requirement, mild to severe organ injury and/or ventricular dysfunction, vasoactive requirement, or ICU admission), 2 mg/kg/dose subcutaneously every 6 hours for 1 day, then 2 mg/kg/dose daily for 4 days (Max: 100 mg/dose) is recommended. (31)
 - In 1 review, authors suggest anakinra 2 to 6 mg/kg/day IV or subcutaneously with the length of therapy to be determined with input from pediatric rheumatology or immunology. (30)
 - Clinical characteristics of 186 pediatric patients meeting criteria for MIS-C have been reported. Thirteen percent of patients received anakinra in addition to IVIG and other therapies. Eighty percent of patients were in the intensive care unit and 20% received mechanical ventilation. As of study end, 70% of patients were discharged alive, 28% were still hospitalized, and 2% had died. (28)
 - On hospital day 4, a 5-year-old patient received treatment with anakinra 4 mg/kg/day and pulse methylprednisolone 30 mg/kg/day after not responding to IVIG 2,000 mg/kg and

methylprednisolone 2 mg/kg/day on hospital day 0 and repeat IVIG on hospital day 2. She was discharged home on hospital day 11. (8)

- In a retrospective study (n = 16, median age 10 years), 1 patient received anakinra 4 mg/kg for respiratory distress. Most patients received IVIG and aspirin. All patients experienced clinical remission after treatment. (25)
- In a retrospective study (n = 35, age 2 to 16 years), 3 patients received anakinra (dose not specified) due to a persistent severe inflammatory state. Most patients in the study received IVIG with and without steroids. Thirty-four patients were discharged after a median hospital stay of 8 days; 5 patients had residual mild to moderate left ventricular systolic dysfunction at last follow-up. (2)
- Safety Concerns: (20)
 - Caution in patients with thrombocytopenia and neutropenia
 - Infusion-related reactions

Adjunctive/Supportive therapy:

Anticoagulation:

- The risk of VTE in MIS-C patients is unknown. One institutional protocol recommends that prophylactic anticoagulation with low molecular weight heparin be considered in critically ill patients and in patients with evidence of activation of coagulation (e.g., elevated D-dimer, high fibrinogen). (4)
- American College of Rheumatology draft guidance recommendation (27):
 - Treatment with low dose aspirin and therapeutic anticoagulation with enoxaparin or warfarin in MIS-C patients with coronary artery aneurysms (CAAs) and a z-score of 10 or more.
 - Therapeutic anticoagulation with enoxaparin is also recommended in patients with a documented thrombosis or an ejection fraction (EF) less than 35%.
 - Continuation is recommended for at least 2 weeks after hospital discharge.
 - Longer outpatient therapeutic enoxaparin may be considered in patients with CAA with z-score of 10 or greater (indefinite treatment), documented thrombosis (treatment for 3 months or more depending on thrombus resolution), or ongoing moderate to severe LV dysfunction.
- Clinical characteristics of 186 pediatric patients meeting criteria for MIS-C have been reported. Forty-seven percent of patients received anticoagulation, defined as heparin, enoxaparin, bivalirudin, warfarin, and argatroban, in addition to IVIG and other therapies. Eighty percent of patients were in the intensive care unit and 20% received mechanical ventilation. As of study end, 70% of patients were discharged alive, 28% were still hospitalized, and 2% had died. (28)
- In a retrospective study (n = 35, age 2 to 16 years), 23 patients received therapeutic dose heparin. None of the patients had a thrombotic or embolic event. (2)

Hemodynamic Support:

- Patients presenting in shock or with unstable vital signs must be aggressively managed. Shock may be cardiogenic or vasodilatory/distributive in nature, and hemodynamic support must be tailored accordingly. (28)
 - One surveillance study of pediatric patients in the United States (n = 186, median age = 8.3 years) reported cardiovascular involvement in 80% of patients. Vasopressor or vasoactive support was required in 90 patients (48%). (28)

Understanding of the management of patients with multisystem inflammatory syndrome in children (MIS-C) is rapidly evolving. Information will continue to emerge regarding pharmacologic management of MIS-C.

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