# Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A

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This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of pediatric patients with multisystem inflammatory syndrome in children (MIS-C). The case definition for MIS-C from the Council of State and Territorial Epidemiologists (CSTE) and the Centers for Disease Control and Prevention includes individuals aged <21 years.[1] The recommendations in this section encompass this age group. There are few randomized controlled trials that directly compared different treatment approaches for MIS-C, and these trials have limitations. Because of those limitations, the Panel's recommendations for the therapeutic management of patients with MIS-C are primarily based on data from large descriptive and observational comparative effectiveness studies. For information on the clinical manifestations of MIS-C, see Special Considerations in Children.

## Multisystem Inflammatory Syndrome in Adults

Adults can present with a syndrome similar to MIS-C, termed multisystem inflammatory syndrome in adults (MIS-A).[2] The published literature on MIS-A is restricted to small case series and observational epidemiologic studies that provide little data to guide treatment decisions in patients with MIS-A.[3-5] Although the therapeutic management of MIS-A has not been studied, it is reasonable to extrapolate from data on treating patients with MIS-C to aid in the management of individuals with MIS-A.

**Table 3d. Therapeutic Management of Hospitalized Patients With MIS-C**

| | Panel's Recommendations |
|---|---|
| **MIS-C** | **Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.**<br>*Initial Immunomodulatory Therapy*<br>• IVIG 2 g/kg IBW IV (up to a maximum total dose of 100 g) **plus** low to moderate dose **methylprednisolone** (1–2 mg/kg/day IV)[a] or another glucocorticoid at an equivalent dose[a] **(AIIb)**.<br>• **Glucocorticoid monotherapy, only** if IVIG is unavailable or contraindicated **(BIIa)**.<br>• **IVIG monotherapy, only** if glucocorticoids are contraindicated **(BIIb)**.<br>*Intensification Immunomodulatory Therapy*<br>• Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of receiving initial immunomodulatory therapy **(AIII)**. One of the following can be used (listed in alphabetical order):<br>  • High-dose **anakinra** 5–10 mg/kg/day IV (preferred) or SUBQ in 1–4 divided doses[b] **(BIIb)**<br>  • Higher-dose **glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV for 1–3 days, up to a maximum of 1,000 mg/day, or equivalent glucocorticoid for 1–3 days)[a,b] **(BIIb)**<br>  • **Infliximab** 5–10 mg/kg IV for 1 dose[b,c] **(BIIb)**<br>*Antithrombotic Therapy*<br>• Low-dose **aspirin** (3–5 mg/kg PO once daily, up to a maximum dose of 81 mg) for all patients without risk factors for bleeding **(AIII)**, **AND**<br>• Anticoagulation for patients who fall under 1 of the following clinical scenarios:<br>  • **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease **(AIII)**.<br>  • **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding **(AIII)**.<br>  • For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis and bleeding. See Table 3e for additional information. |
| Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information. | |

[a] The duration of glucocorticoid therapy may vary. When a patient shows clinical improvement (e.g., resolution of fever, improvement of organ function, reduction of levels of inflammatory markers), a steroid taper should be initiated. Typically, the patient's clinical status guides the taper, and it continues for several weeks to avoid rebound inflammation. See Table 3e and text below.

[b] In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids plus anakinra **(BIII)** or higher-dose glucocorticoids plus infliximab **(BIII)**. **Anakinra and infliximab should not be used in combination**.

[c] **Infliximab should not be used** in patients with macrophage activation syndrome.

**Key:** CAA = coronary artery aneurysm; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LV = left ventricular; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SUBQ = subcutaneous

**Table 3e. Dosing Regimens for the Drugs Recommended for the Treatment of MIS-C**

| | **Dosing Regimens**<br>*For infants, children, and adolescents unless otherwise specified.*<br>*The doses listed are for FDA-approved indications for other diseases or from reported experiences or clinical trials.* | **Adverse Events** | **Monitoring Parameters** |
|---|---|---|---|
| **Intravenous Immunoglobulin** | IVIG 2 g/kg IBW IV (up to a maximum total dose of 100 g)<br>In the event of cardiac dysfunction or fluid overload, consider administering IVIG in divided doses (i.e., IVIG 1 g/kg IBW IV, up to 50 g daily for 2 doses). | • Hypersensitivity<br>• Fever<br>• Chills<br>• Flushing<br>• Hemolytic anemia | • Renal function<br>• Urine output<br>• CBC with differential<br>• Infusion-related AEs<br>• Anaphylaxis<br>• Signs and symptoms of hemolysis |
| **Methyl-prednisolone** | Methylprednisolone 1–2 mg/kg IV every 12 hours<br>Intensification immunomodulatory therapy: If the patient does not respond to 1–2 mg/kg IV every 12 hours, increase the dose to 10–30 mg/kg/day IV for 1–3 days (up to a maximum of 1,000 mg/day).<br>Glucocorticoids should be tapered gradually after signs of clinical improvement. The duration of the taper will depend on the patient's clinical status. | • Adrenal suppression<br>• Hyperglycemia<br>• Sodium retention<br>• Fluid retention<br>• Leukocytosis<br>• Immune suppression<br>• Psychiatric disturbances | • Blood pressure<br>• CBC with differential<br>• BMP |
| **Anakinra** | Anakinra 5–10 mg/kg/day IV (preferred) or SUBQ in 1 to 4 divided doses | • Headache<br>• Fever<br>• Hypersensitivity<br>• Immune suppression<br>• Transaminase elevation<br>• Injection site reactions (for SUBQ) | • CBC with differential<br>• LFTs<br>• SCr |
| **Infliximab** | Infliximab 5–10 mg/kg IV for 1 dose | • Infusion-related reaction<br>• Headache<br>• Immune suppression | • Monitor vital signs every 2–10 minutes during infusion.<br>• CBC with differential |
| **Aspirin** | Aspirin 3–5 mg/kg PO once daily (up to a maximum of 81 mg) | • Gastrointestinal ulcers<br>• Hypersensitivity | • Signs or symptoms of bleeding<br>• Renal function |
| **Enoxaparin** | **For Prophylaxis**<br>*Aged >2 Months to <18 Years*<br>• 0.5 mg/kg SUBQ every 12 hours (up to maximum of 30 mg)<br>**For Treatment**<br>*Aged >2 Months to <18 Years*<br>• 1 mg/kg SUBQ every 12 hours<br>• Monitor antifactor Xa activity (treatment goal: 0.5–1 unit/mL). | • Increased risk of bleeding | • CBC with differential<br>• Renal function |

**Key:** AE = adverse event; BMP = basic metabolic panel; CBC = complete blood count; FDA = Food and Drug Administration; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SCr = serum creatinine; SUBQ = subcutaneous

## Treatment Considerations for Children With MIS-C

### *Initial Immunomodulatory Therapy for MIS-C*

The Panel recommends consulting with a multidisciplinary team when managing immunomodulatory therapy for children with MIS-C **(AIII)**. The multidisciplinary team may include experts in cardiology, hematology, infectious disease, intensive care, and rheumatology. MIS-C is defined by multiorgan dysfunction, and input from other pediatric subspecialists may be needed depending on the presentation of the individual patient. Thus, children with MIS-C should be cared for at centers with access to these pediatric specialists.

Intravenous immunoglobulin (IVIG) and glucocorticoids are the most commonly used immunomodulatory medications in reported cohorts of children with MIS-C.[6-14] The American College of Rheumatology has outlined initial diagnostic and treatment considerations for patients with MIS-C and recommends using IVIG in combination with glucocorticoids as first-tier therapy for most hospitalized children with MIS-C.[15] Several nonrandomized studies suggest that the use of IVIG plus glucocorticoids is associated with less treatment failure, faster recovery of cardiac function, shorter intensive care unit (ICU) stays, and less need for treatment escalation than IVIG monotherapy.[7,16-22] Based on these data, the Panel recommends using **IVIG** in combination with low to moderate doses of glucocorticoids for children hospitalized with MIS-C **(AIIb)**.

IVIG should be administered at a dose of 2 g/kg of ideal body weight, with a maximum total dose of 100 g. The patient's cardiac function and fluid status should be monitored carefully during the IVIG infusion. IVIG can be given in divided doses of 1 g/kg of ideal body weight over 2 days if there is a concern about the patient's fluid status. Methylprednisolone 1 to 2 mg/kg/day, or another glucocorticoid at an equivalent dose, is considered low to moderate glucocorticoid dosing. When the patient has improved clinically (e.g., when the patient is afebrile, end-organ dysfunction resolves, and inflammatory markers trend downward), a steroid taper should be initiated. Typically, the patient's clinical status guides the taper, and it continues for several weeks to avoid rebound inflammation.

Glucocorticoid monotherapy is an alternative initial treatment for MIS-C. Some studies have shown that patients treated with this approach had similar outcomes to patients treated with IVIG monotherapy or IVIG plus glucocorticoids.[18,20,23,24] However, secondary analyses indicate that patients who were initially treated with IVIG plus glucocorticoids had faster time to improvement, less need for treatment escalation, and faster time to defervescence than patients who received glucocorticoid monotherapy.[20] Thus, the combination of IVIG and glucocorticoids appears to provide additional benefits that are not provided by glucocorticoid monotherapy.

Initial treatment that includes IVIG is also beneficial because it reduces the frequency of coronary artery aneurysms (CAAs) in patients with Kawasaki disease.[14,25] Kawasaki disease is increasingly difficult to differentiate from MIS-C, and more recent SARS-CoV-2 variants have resulted in MIS-C presentations that are similar to Kawasaki disease.[26] Distinguishing MIS-C from Kawasaki disease is further complicated by the fact that seropositivity for SARS-CoV-2 is now widespread, which makes establishing the epidemiological link required for the MIS-C diagnosis difficult. For these reasons, the Panel recommends using **IVIG** plus glucocorticoids as the initial therapy for patients with MIS-C **(AIIb)**. **Glucocorticoid monotherapy** is recommended **only** if IVIG is unavailable or contraindicated **(BIIa)**. **IVIG monotherapy** is recommended **only** if glucocorticoids are contraindicated **(BIIb)**.

### *Clinical Data on Initial Immunomodulatory Therapy for MIS-C*

#### Intravenous Immunoglobulin in Combination With Glucocorticoids

No randomized clinical trials evaluating the use of IVIG plus glucocorticoids for the treatment of MIS-C

have been completed. The comparative benefit of adding steroids to IVIG for MIS-C treatment has been estimated in observational cohort studies that used statistical techniques to adjust for confounders. The first of these studies employed observational data from a national surveillance system cohort in France and used propensity matching to compare short-term outcomes in children with MIS-C who were treated initially with IVIG 2 gm/kg alone or IVIG plus methylprednisolone (most patients received 1.6–2 mg/kg/day for 5 days).[16] The study team observed a lower risk of treatment failure (defined as a fever that persisted for 2 days after treatment or recurrent fever within 7 days), less need for hemodynamic support, less severe left ventricular dysfunction, and shorter ICU stays among the children who were initially treated with the combination therapy. This was a small study, and only 32 patients treated with IVIG plus methylprednisolone and 64 patients treated with IVIG alone could be matched based on propensity score.

A larger study in the United States analyzed data from the Overcoming COVID-19 surveillance registry to evaluate immunomodulatory therapy for MIS-C.[17] The study included 103 patients who received initial treatment with IVIG plus glucocorticoids and an equal number of propensity score–matched patients who received IVIG alone. The risk of cardiovascular dysfunction on or after Day 2 was measured among these patients using a composite outcome of left ventricular ejection fraction of <55% or vasopressor use. The composite outcome occurred in 17% of patients in the IVIG plus glucocorticoids arm and in 31% of patients in the IVIG alone arm (risk ratio 0.56; 95% CI, 0.34–0.94). In addition, patients treated with the combination of IVIG and glucocorticoids were less likely to require adjunctive immunomodulatory therapy than those treated with IVIG alone. Methylprednisolone, the glucocorticoid that was prescribed most often, was administered to 353 patients (68% of patients, including nonpropensity score–matched patients, in the entire cohort). Among these patients, the dosing of methylprednisolone ranged from 2 mg/kg/day in 284 patients (80%) to 10 to 30 mg/kg/day in 69 patients (20%).

A third study, the international, observational BATS study, compared patients with MIS-C who received IVIG alone (n = 246) with those who received IVIG plus glucocorticoids (n = 208).[18] This study found similar rates for the composite outcome of inotropic support or mechanical ventilation by Day 2 or later or death in both treatment arms. The composite outcome occurred in 44 of 221 patients (21%) in the IVIG alone arm and in 56 of 180 patients (31%) in the IVIG plus glucocorticoids arm (OR 0.77; 95% CI, 0.33–1.82). However, escalation of immunomodulatory treatment was less common among the patients who received IVIG plus glucocorticoids than among those who received IVIG alone (OR 0.18; 95% CI, 0.10–0.33). Notably, the study allowed for the inclusion of patients who had any inflammatory illness after acute COVID-19 but who did not meet the Centers for Disease Control and Prevention or World Health Organization (WHO) criteria for MIS-C. This multicenter study included sites from 34 countries, which introduced the potential for more variability in supportive care. In addition, the overall percentage of patients with abnormal cardiac findings (12% of the 538 patients) was lower than in other cohorts.

### Intravenous Immunoglobulin Monotherapy

The use of IVIG is long established for patients with Kawasaki disease, a syndrome that has overlapping manifestations with MIS-C. Thus, the product's safety profile is well understood. In patients with Kawasaki disease, IVIG reduces the development of CAAs,[25,27] a complication also observed in some patients with MIS-C. IVIG is the most frequently used therapy for MIS-C. In a national survey of U.S. institutional protocols for managing MIS-C, IVIG was the first-line therapy in 98% of 40 participating centers.[28]

Data on the efficacy of IVIG in patients with MIS-C is extrapolated from case series that show mostly favorable outcomes. In a series of 539 MIS-C cases, 77% of the children received IVIG.[14] A sizeable proportion of these children had reduced left ventricular ejection fraction at admission (172 of 503 evaluable patients [34.2%]). The symptom resolved by Day 30 in 156 of the children (90.7%). Although these studies have not described the occurrence of specific adverse events related to IVIG use, the

dosing used (IVIG 2 g/kg) has a well-established safety profile when used for Kawasaki disease.

A limitation of all published studies on IVIG use for MIS-C is the frequent and often rapid sequential addition of other immunomodulatory therapies, such as corticosteroids. In addition, there is accumulating evidence that glucocorticoids administered in combination with IVIG are more effective as treatment for MIS-C. However, IVIG monotherapy may be a reasonable treatment option for a small subset of patients with MIS-C who are stable (i.e., not in shock or with organ-threatening disease) and have contraindications for glucocorticoid therapy. Such contraindications may include concern about the impact of corticosteroids on the diagnostic evaluation or an underlying medical condition.

### Glucocorticoid Monotherapy

The observational BATS study also compared initial IVIG monotherapy treatment (n = 246) with glucocorticoid treatment (n = 99) and found no differences in primary or secondary outcomes between these 2 cohorts.[18] However, in a subgroup analysis of patients who met the WHO criteria for MIS-C, the glucocorticoid arm (n = 78) had significantly fewer patients who required respiratory support by Day 2 or later or died than the IVIG arm (n = 192).

In a subsequent publication, the BATS consortium reported on additional patients with MIS-C who were enrolled in the study (over 2,000 patients in total).[20] The study had 2 primary outcomes. The first was a composite of the need for inotropic or ventilator support on or after Day 2 or death. The second was time to improvement by 1 level on an ordinal severity scale. In this larger study, there was once again no difference in the primary outcomes among the arms in a propensity-weighted analysis (combination therapy with IVIG plus glucocorticoids was compared to IVIG alone, and glucocorticoid monotherapy was compared to IVIG alone).

In secondary analyses, patients who received combination therapy had a lower rate of treatment escalation than those who received IVIG alone, and patients who received glucocorticoid monotherapy had a lower rate of treatment escalation than those who received IVIG alone.[20] The combination therapy arm had a faster time to improvement, less need for treatment escalation, and a lower rate of persistent fever on Day 2 than the glucocorticoid monotherapy arm. These treatment arms had similar frequencies of CAAs measured at hospital discharge and similar CAA severity. Among the 236 patients with documented CAAs during the initial hospitalization, 196 patients had follow-up echocardiograms. More than 90% of the CAAs resolved, with similar rates of resolution across the treatment groups.

As reported in the initial publication for the observational BATS study, the inclusion criteria were broad, and the patients did not need to meet the full WHO case definition for MIS-C.[20] Compared to the other treatment arms, the IVIG plus glucocorticoid arm had a greater proportion of patients that met the WHO case definition for MIS-C, were ventilated and/or treated with inotropes at Day 0, and had CAAs (even before the initiation of immunomodulators). Many patients received additional immunomodulatory agents after Day 1, including 230 of 487 patients in the initial glucocorticoids alone group who also received IVIG. Finally, COVID-19 vaccination has been associated with reduced incidence and severity of MIS-C,[29-31] but vaccination was not evaluated in the study.

To date, the only randomized trial that evaluated treatments in patients with MIS-C was conducted in Switzerland.[23] This open-label, multicenter study compared methylprednisolone 10 mg/kg per day for 3 days (n = 37) to a single dose of IVIG 2 gm/kg (n = 38). In this study, patients met the criteria for the case definition of pediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV-2 (PIMS-TS). There was no difference between the arms for the primary outcome of length of hospital stay or death. The length of hospital stay from admission to discharge was 6 days for both arms (estimated effect size -0.037 of the $\log_{10}$ transformed times; 95% CI, -0.13 to 0.065; $P = 0.42$). No deaths were reported in either arm.

In a secondary analysis, 27% of patients in the glucocorticoid arm required respiratory support compared to 55% of those in the IVIG arm, which was a statistically significant result.[23] There was no difference between the arms for the occurrence of coronary artery enlargement. The small sample size in this study limited the power for treatment comparisons, and many patients received additional therapies for MIS-C after randomization.

## Intensification Immunomodulatory Therapy for MIS-C

Children with MIS-C typically respond briskly to immunomodulatory therapy and show clinical improvements within the first 24 hours of treatment. Treatment response is characterized by resolution of fever, improvement of organ function, and reduction of levels of inflammatory markers, particularly C-reactive protein. In contrast, refractory disease is often accompanied by persistent fever, worsening organ dysfunction, and increasing levels of inflammatory markers. Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of receiving initial immunomodulatory therapy **(AIII)**. Children with uncontrolled MIS-C despite treatment with IVIG and low to moderate doses of glucocorticoids will often continue to deteriorate, and this decline in clinical status can be quite rapid.

No studies have compared the different intensification therapies used for patients with MIS-C. The data on this topic are limited to results from cohort studies in patients with MIS-C, opinions from experts, and clinician experiences treating children with other hyperinflammatory syndromes, such as Kawasaki disease and macrophage activation syndrome. For children with refractory MIS-C, the Panel recommends providing additional immunomodulatory therapy (listed in alphabetical order) with **high-dose anakinra (BIIb)**, **higher-dose glucocorticoids (BIIb)**, or **infliximab (BIIb)**. Currently, there is insufficient evidence to determine which of these agents is most effective for intensification therapy in patients with refractory MIS-C. In certain patients with severe illness, intensification therapy may include dual therapy with **higher-dose glucocorticoids** plus **anakinra (BIII)** or **higher-dose glucocorticoids** plus **infliximab (BIII)**. **Anakinra and infliximab should not be used in combination.** A second dose of IVIG is not commonly reported in the literature as a strategy for intensification therapy in patients with MIS-C. This may be due to the high rates of IVIG resistance, the rapid pace of disease escalation, and the risk for fluid overload in patients with MIS-C.[10] Therefore, the Panel **recommends against** a second dose of **IVIG** for intensification therapy in patients with refractory MIS-C **(BIII)**.

Patients with MIS-C who receive multiple immunomodulatory agents are at risk for infection and need to be monitored carefully. Most children with MIS-C were previously healthy. In patients who have an immune disorder or are taking immunosuppression therapy, the risk of infection is greater. The risks and benefits of using immunomodulatory agents in patients with MIS-C who are immunocompromised need to be evaluated on a case-by-case basis.

### *Clinical Data on Intensification Immunomodulatory Therapy for MIS-C*

#### High-Dose Glucocorticoids

The use of high-dose glucocorticoids in pediatric patients with other inflammatory conditions, such as Kawasaki disease and macrophage activation syndrome, is well established.[32,33] High-dose glucocorticoid therapy is defined as intravenous (IV) administration of 10 to 30 mg/kg/day of methylprednisolone (or an equivalent corticosteroid). Often, this higher dose of glucocorticoids is administered for 1 to 3 days before returning to low to moderate doses (1–2 mg/kg/day). Multiple observational studies have evaluated the use of high-dose glucocorticoids in children with MIS-C.[17,34] In addition, single-center treatment protocols for MIS-C that incorporate high-dose glucocorticoids into the treatment algorithm have been published.[19] Implementation of the protocols has resulted in positive clinical outcomes in patients with MIS-C.

### Anakinra

Anakinra is the most commonly used biologic medication for the treatment of MIS-C in the United States.[28] Multiple noncomparative, observational cohorts have reported on the use of anakinra in patients with MIS-C.[10,11,13,35-39] This medication has been used extensively and has a good safety record in pediatric patients with other hyperinflammatory syndromes (e.g., systemic juvenile idiopathic arthritis, macrophage activation syndrome).[40-42] Anakinra has also been used successfully to treat IVIG-resistant Kawasaki disease. Anakinra has a short half-life (4–6 hours), and the medication can be stopped quickly, which many providers regard as a benefit relative to longer-acting immunomodulators. The Panel's recommendation for the use of high-dose anakinra (5–10 mg/kg/day) in patients with MIS-C is based on the demonstrated efficacy of high-dose anakinra in patients with macrophage activation syndrome. The duration of anakinra therapy varies in the literature. Some clinicians prescribe anakinra as a steroid-sparing agent to manage MIS-C for longer periods (e.g., up to 2 weeks).

### Infliximab

The Panel recommends a single dose of infliximab 5 to 10 mg/kg IV as an option for intensification therapy. Infliximab has been studied for the treatment of MIS-C in a single-center retrospective study that compared patients treated with IVIG alone (n = 20) to those treated with IVIG and a single dose of infliximab 10 mg/kg IV (n = 52).[43] Infliximab was used as the first-line therapy in this study, and the patients were not treated with glucocorticoids. The patients who received IVIG and infliximab were more likely to be admitted to the ICU and had more severe illness than those who received IVIG alone. However, the patients who received the combination therapy were less likely to require additional therapy after 24 hours (the primary outcome). In addition, patients who received IVIG and infliximab had shorter stays in the ICU and improved cardiac outcomes. These results suggest that infliximab has a therapeutic effect in patients with MIS-C.

Infliximab is approved by the Food and Drug Administration for use in children with inflammatory bowel disease and is used widely to treat juvenile idiopathic arthritis. Infliximab has also been used to treat IVIG-resistant Kawasaki disease.[44,45] Although the half-life of infliximab in patients with MIS-C is unknown, it likely has effects that persist for several weeks. This extended period of drug activity may provide a steroid-sparing effect in patients with MIS-C.

## Antithrombotic Therapy for MIS-C

The Panel recommends the use of **low-dose aspirin** for patients with MIS-C who do not have risk factors for bleeding **(AIII)**. This recommendation is largely derived from experience treating children with Kawasaki disease and the increased likelihood of analogous platelet activation and endothelial dysfunction in children with MIS-C.[46] Children treated with aspirin and steroids should also receive prophylactic H2 blockers or proton pump inhibitors. Patients with MIS-C who have large CAAs (Z-score ≥10) should receive **therapeutic anticoagulation** according to the American Heart Association guidelines for Kawasaki disease **(AIII)**. Children with left ventricular dysfunction are at risk for intracardiac thrombosis. Patients with MIS-C and moderate to severe left ventricular dysfunction who have no risk factors for bleeding should receive **therapeutic anticoagulation (AIII)**.

There is less consensus on the use of either prophylactic or therapeutic anticoagulation in patients with MIS-C who do not have large CAAs or moderate to severe left ventricular dysfunction. Children with MIS-C have marked elevations in D-dimer levels and other abnormalities of coagulation, which suggests that they may be at increased risk for thrombosis.[47] In a multicenter retrospective study of children with acute COVID-19 and MIS-C, the independent risk factors for thrombosis included indwelling catheters, older age (>12 years), malignancy, admission to the ICU, and elevated D-dimer levels.[48] In a multicenter, Phase 2 trial of enoxaparin thromboprophylaxis in children hospitalized for COVID-19 and MIS-C

(COVAC-TP), children with MIS-C frequently exhibited hyperfibrinogenemia and had significantly elevated D-dimer levels compared to children with primary SARS-CoV-2 infection.[49]

Published data on the risk of bleeding in children with MIS-C who are managed with anticoagulant thromboprophylaxis are limited. Major bleeding events (as defined by the International Society on Thrombosis and Haemostasis) were observed in patients with MIS-C who were treated with anticoagulation in the aforementioned retrospective study[48] but not in the COVAC-TP trial, which employed prophylactic dosing of enoxaparin and permitted the use of aspirin at a dose of up to 5 mg/kg/day.[49] However, 5% of patients developed catheter-related thromboembolic events despite the use of enoxaparin thromboprophylaxis in the COVAC-TP trial.

Given the uncertainty regarding the benefit of anticoagulation in the treatment of MIS-C, prophylactic or therapeutic anticoagulation for children with MIS-C who do not have large CAAs or moderate to severe left ventricular dysfunction should be considered on a case-by-case basis, taking into account the risk factors for thrombosis and bleeding.

## Antiviral Therapy for MIS-C

The role of SARS-CoV-2 antiviral therapy in treating MIS-C has not been systematically studied. However, it is not expected to be beneficial because MIS-C is considered an immune-mediated phenomenon that occurs weeks after primary SARS-CoV-2 infection. Therefore, the Panel **recommends against** the use of SARS-CoV-2 antiviral therapy for patients with MIS-C **(AIII)**.

## Critical Care Management

Shock occurs in approximately 50% of patients with MIS-C and may include elements of distributive, cardiogenic, or hypovolemic shock.[14,50,51] In general, clinicians should manage shock in patients with MIS-C per the usual critical care standards outlined in the pediatric Surviving Sepsis Campaign guidelines.[52]

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