



# 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 (CDC) includes individuals aged <21 years.<sup>1</sup> The recommendations in this section encompass this age group. No randomized controlled trials have compared different treatment approaches for MIS-C. However, data from descriptive and observational comparative effectiveness studies are available to guide treatment for MIS-C. For information on the clinical manifestations of MIS-C, see [Special Considerations in Children](#).

## Multisystem Inflammatory Syndrome in Adults

It should be noted that adults can present with a syndrome similar to MIS-C, termed multisystem inflammatory syndrome in adults (MIS-A).<sup>2</sup> The published literature on MIS-A is restricted to small case series and a single observational epidemiological study that provide little data to guide treatment decisions for patients with MIS-A.<sup>3-5</sup> 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 Pediatric Patients With MIS-C**

	Panel's Recommendations
<b>MIS-C</b>	<p><b>Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.</b></p> <p><i>Initial Immunomodulatory Therapy</i></p> <ul style="list-style-type: none"> <li>• <b>IVIG</b> 2 g/kg IBW (up to a maximum total dose of 100 g) IV <b>plus</b> low to moderate dose <b>methylprednisolone</b> (1–2 mg/kg/day) IV<sup>a</sup> or another glucocorticoid at an equivalent dose<sup>a</sup> (<b>AIIb</b>).</li> <li>• <b>Glucocorticoid monotherapy, only</b> if IVIG is unavailable or contraindicated (<b>BIIa</b>).</li> <li>• <b>IVIG monotherapy, only</b> if glucocorticoids are contraindicated (<b>BIIb</b>).</li> </ul> <p><i>Intensification Immunomodulatory Therapy</i></p> <ul style="list-style-type: none"> <li>• Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of receiving initial immunomodulatory therapy (<b>AIII</b>). One of the following can be used (listed in alphabetical order):             <ul style="list-style-type: none"> <li>• High-dose <b>anakinra</b> 5–10 mg/kg IV or SUBQ once daily (<b>BIIb</b>)</li> <li>• Higher-dose <b>glucocorticoid</b> (e.g., <b>methylprednisolone</b> 10–30 mg/kg/day IV or equivalent glucocorticoid) (<b>BIIb</b>)<sup>b</sup></li> <li>• <b>Infliximab</b><sup>c</sup> 5–10 mg/kg IV for 1 dose (<b>BIIb</b>)</li> </ul> </li> </ul> <p><i>Antithrombotic Therapy</i></p> <ul style="list-style-type: none"> <li>• Low-dose <b>aspirin</b> (3–5 mg/kg/day, up to maximum dose of 81 mg/day) PO for all patients without risk factors for bleeding (<b>AIII</b>), <b>AND</b></li> <li>• Anticoagulation for patients who fall under 1 of the following clinical scenarios:             <ul style="list-style-type: none"> <li>• <b>Therapeutic anticoagulation</b> for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease (<b>AIII</b>).</li> <li>• <b>Therapeutic anticoagulation</b> for patients with moderate to severe LV dysfunction who have no risk factors for bleeding (<b>AIII</b>).</li> <li>• For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider <b>prophylactic or therapeutic anticoagulation</b> on an individual basis, taking into consideration risk factors for thrombosis and bleeding. See Table 3e for additional information.</li> </ul> </li> </ul>
<p>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 <a href="#">Guidelines Development</a> for more information.</p>	

<sup>a</sup> Duration of therapy may vary. See Table 3e and text below.

<sup>b</sup> In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

<sup>c</sup> 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 = subcutaneously

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

	<b>Dosing Regimens</b>		
	<p><i>For infants, children, and adolescents unless otherwise specified.</i></p> <p><i>The doses listed are for FDA-approved indications for other diseases or from reported experiences or clinical trials.</i></p>	<b>Adverse Events</b>	<b>Monitoring Parameters</b>
<b>Intravenous Immunoglobulin</b>	<p>IVIg 2 g/kg IBW (up to a maximum total dose of 100 g) IV</p> <p>In the event of cardiac dysfunction or fluid overload, consider administering IVIg in divided doses (1 g/kg IBW per dose IV every 24 hours for 2 doses).</p>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Fever</li> <li>• Chills</li> <li>• Flushing</li> <li>• Hemolytic anemia</li> </ul>	<ul style="list-style-type: none"> <li>• Renal function</li> <li>• Urine output</li> <li>• CBC with differential</li> <li>• Infusion or injection-related AEs</li> <li>• Anaphylaxis</li> <li>• Signs and symptoms of hemolysis</li> </ul>
<b>Methyl-prednisolone</b>	<p>Methylprednisolone 1–2 mg/kg IV every 12 hours</p> <p>If the patient does not respond to 1–2 mg/kg IV every 12 hours, increase the dose to 10–30 mg/kg/day (up to maximum of 1,000 mg/day) IV for 1–3 days.</p>	<ul style="list-style-type: none"> <li>• Adrenal suppression</li> <li>• Hyperglycemia</li> <li>• Sodium retention</li> <li>• Fluid retention</li> <li>• Leukocytosis</li> <li>• Immune suppression</li> </ul>	<ul style="list-style-type: none"> <li>• Blood pressure</li> <li>• CBC with differential</li> <li>• BMP</li> </ul>
<b>Anakinra</b>	<p>Anakinra 5–10 mg/kg/day IV (preferred) or SUBQ in 1 to 4 divided doses</p>	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Fever</li> <li>• Hypersensitivity</li> <li>• Immune suppression</li> <li>• Transaminitis</li> </ul>	<ul style="list-style-type: none"> <li>• CBC with differential</li> <li>• LFTs</li> <li>• SCr</li> </ul>
<b>Infliximab</b>	<p>Infliximab 5–10 mg/kg IV for 1 dose</p>	<ul style="list-style-type: none"> <li>• Infusion-related reaction</li> <li>• Headache</li> <li>• Immune suppression</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor vital signs every 2–10 minutes during infusion.</li> <li>• CBC with differential</li> </ul>
<b>Aspirin</b>	<p>Aspirin 3–5 mg/kg (up to maximum of 81 mg) PO once daily</p>	<ul style="list-style-type: none"> <li>• Gastrointestinal ulcers</li> <li>• Hypersensitivity</li> <li>• Renal dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>• Signs or symptoms of bleeding</li> <li>• Renal function</li> </ul>
<b>Enoxaparin</b>	<p><b>Enoxaparin Prophylaxis</b></p> <p><i>Aged &gt;2 Months to &lt;18 Years</i></p> <ul style="list-style-type: none"> <li>• 0.5 mg/kg (up to maximum of 30 mg) SUBQ every 12 hours</li> </ul> <p><b>Enoxaparin Treatment</b></p> <p><i>Aged &gt;2 Months to &lt;18 Years</i></p> <ul style="list-style-type: none"> <li>• 1 mg/kg SUBQ every 12 hours</li> <li>• Monitor antifactor Xa activity (treatment goal: 0.5 to 1).</li> </ul>	<ul style="list-style-type: none"> <li>• Increased risk of bleeding</li> <li>• Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• CBC with differential</li> <li>• Renal function</li> </ul>

**Key:** AE = adverse effect; BMP = blood mineral 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.<sup>6-14</sup> 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.<sup>15</sup> 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.<sup>7,16-20</sup> 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 given 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. Once there is clinical improvement (i.e., the child is afebrile, end organ dysfunction resolves, and inflammatory markers are trending downward), a steroid taper should be initiated. Typically, the taper lasts for several weeks to avoid rebound inflammation and is guided by the clinical status of the patient.

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 and IVIG plus glucocorticoids.<sup>18,20,21</sup> 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.<sup>20</sup> 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.<sup>14,22</sup> 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.<sup>23</sup> Distinguishing MIS-C from Kawasaki disease is further complicated by the fact that seropositivity for SARS-CoV-2 is now widespread, making it difficult to establish the epidemiological link required for the MIS-C diagnosis. 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 (**BIIfa**). **IVIG monotherapy** is recommended **only** if glucocorticoids are contraindicated (**BIIfb**).

## 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).<sup>16</sup> 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.<sup>16</sup> 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. 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).<sup>17</sup> 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) to those who received IVIG plus glucocorticoids (n = 208). 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). It is notable that the study also allowed for the inclusion of patients who had any inflammatory illness after acute COVID-19 but who did not meet the CDC 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.<sup>18</sup>

### **Intravenous Immunoglobulin Monotherapy**

The use of IVIG is long established for patients with Kawasaki disease, a syndrome that has overlapping manifestations with MIS-C, and thus the product's safety profile is well understood. In patients with Kawasaki disease, IVIG prevents the development of CAAs,<sup>22,24</sup> 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.<sup>25</sup>

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. 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.<sup>14</sup>

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 given 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 treatment with IVIG (n = 246) to treatment with glucocorticoids (n = 99) and found no differences in primary or secondary outcomes between these 2 cohorts.<sup>18</sup> 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 who 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).<sup>20</sup> 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, there were lower rates of treatment escalation among patients who received combination therapy than among those who received IVIG alone, and lower rates of treatment escalation among patients who received glucocorticoid monotherapy than among those who received IVIG alone. There was faster time to improvement, less need for treatment escalation, and lower rates of persistent fever on Day 2 in the combination therapy arm compared to the glucocorticoid monotherapy arm. The frequency of CAAs measured at hospital discharge and the severity of CAAs were similar in these treatment arms. Of the 236 patients with documented CAAs during the initial hospitalization, 196 had follow-up echocardiograms. Over 90% of the CAAs resolved, with similar rates of resolution across the treatment groups.

As in the initial publication for the observational BATS study, the inclusion criteria are broad and the patients did not need to meet the full WHO case definition for MIS-C. Compared to the other treatment arms, a greater proportion of the patients in the IVIG plus glucocorticoid arm 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, but this was not evaluated in the study.<sup>26,27</sup>

To date, the only randomized trial that evaluated treatments in patients with MIS-C was conducted in Switzerland.<sup>21</sup> 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 multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 (PMIS-TS). There was no difference in the primary outcome of length of hospital stay or death between the 2 arms. 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 treated with IVIG, which was a significant difference. There was no difference in the occurrence of coronary artery enlargement between the 2 arms. 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 reduced 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 without further intervention, and this decline in clinical status can be quite rapid.

No comparative studies have evaluated intensification therapies for MIS-C. The data on this topic are limited to results from cohort studies in patients with MIS-C, expert opinion, and experience in treating other hyperinflammatory syndromes in children, such as Kawasaki disease and macrophage activation syndrome. For children with refractory MIS-C, the Panel recommends providing additional immunomodulatory therapy (in alphabetical order) with **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 patients with refractory severe disease, some Panel members would use dual therapy with **higher-dose glucocorticoids** and **anakinra (BIII)** or **higher-dose glucocorticoids** and **infliximab (BIII)** for intensification therapy. 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.<sup>10</sup> 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

High-dose glucocorticoid therapy is defined as methylprednisolone (or an equivalent corticosteroid) dosed at 10 to 30 mg/kg/day and given intravenously (IV). Often, this higher dose of glucocorticoids is given 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 (methylprednisolone 10–30 mg/kg/day) in children with MIS-C.<sup>17,28–30</sup> In addition, single-center treatment protocols for MIS-C that incorporate high-dose glucocorticoids into the treatment algorithm have been published. Implementation of the protocols has resulted in positive clinical outcomes in patients with MIS-C.<sup>19</sup> There is substantial experience with using high-dose glucocorticoids in pediatric patients with other inflammatory

conditions, such as Kawasaki disease and macrophage activation syndrome.

### Anakinra

Anakinra is the most commonly used biologic medication for the treatment of MIS-C in the United States.<sup>25</sup> Multiple noncomparative, observational cohorts have reported on the use of anakinra in patients with MIS-C.<sup>10,11,13,31-33</sup> 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).<sup>34-36</sup> 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. High-dose anakinra (5–10 mg/kg/day) is recommended for patients with MIS-C based on the demonstrated efficacy of high-dose anakinra in patients with macrophage activation syndrome. The duration of anakinra therapy varies in the literature and is used by some patients for long periods (e.g., up to 2 weeks) as a steroid-sparing agent.

### 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).<sup>37</sup> Of note, 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 show 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 been employed in IVIG-resistant Kawasaki disease.<sup>38,39</sup> 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 can allow for a steroid-sparing effect in patients with MIS-C.

## Antithrombotic Therapy for MIS-C

There is general agreement that patients with MIS-C who do not have risk factors for bleeding should receive low-dose aspirin (**AIII**). This recommendation is largely due to experience in treating children with Kawasaki disease and the likelihood of analogous platelet activation and endothelial dysfunction in children with MIS-C.<sup>40</sup> 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  $\geq 10$ ) 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 should receive therapeutic anticoagulation, unless it is contraindicated due to bleeding risk factors (**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 and/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.<sup>41</sup> 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.<sup>42</sup> 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.<sup>43</sup> There are limited published data on the risk of bleeding in children with MIS-C who are managed with anticoagulant thromboprophylaxis. 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<sup>42</sup> 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.<sup>43</sup> 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 for 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.<sup>14,44,45</sup> In general, clinicians should manage shock in patients with MIS-C per the usual critical care standards as outlined in the Pediatric Surviving Sepsis Campaign Guidelines.<sup>46</sup>

### References

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