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Original Article

# Management of Multisystem Inflammatory Syndrome in Children Associated With COVID-19: A Survey From the International Kawasaki Disease Registry

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## ABSTRACT

**Background:** Since April 2020, there have been numerous reports of children presenting with systemic inflammation, often in critical condition, and with evidence of recent infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This condition, since defined as the multisystem inflammatory syndrome in children (MIS-C), is assumed to be a delayed immune response to coronavirus disease 2019 (COVID-19), and there are frequently cardiac manifestations of ventricular dysfunction and/or coronary artery dilation.

**Methods:** We surveyed the inpatient MIS-C management approaches of the members of the International Kawasaki Disease Registry across 38 institutions and 11 countries.

**Results:** Among the respondents, 56% reported using immunomodulatory treatment for all MIS-C patients, regardless of presentation.

## RÉSUMÉ

**Contexte :** Depuis avril 2020, de nombreux cas d'enfants présentant une inflammation généralisée, se trouvant souvent dans un état critique et montrant des signes d'une infection récente au coronavirus du syndrome respiratoire aigu sévère 2 (SRAS-CoV-2), ont été signalés. On pense que cet état, désigné depuis sous le nom de *syndrome inflammatoire multi-systémique de l'enfant* (SIME), pourrait être une réponse immunitaire tardive au virus de la maladie à coronavirus 2019 (COVID-19); les patients présentent souvent des manifestations cardiaques associées à une dysfonction ventriculaire ou à une dilatation des artères coronaires.

**Méthodologie :** Nous avons mené un sondage sur les stratégies de prise en charge du SIME en milieu hospitalier auprès des membres du registre international de la maladie de Kawasaki, qui sont rattachés à 38 établissements répartis dans 11 pays.

In April 2020, the National Health Service in the United Kingdom alerted the medical community of children presenting critically ill with findings similar to Kawasaki disease (KD) or toxic shock syndrome in the setting of recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.<sup>1</sup> This syndrome was later referred to as pediatric multisystem inflammatory syndrome (PIMS) and multisystem

inflammatory syndrome in children (MIS-C), with several proposed case definitions (Table 1).<sup>2-4</sup> Since that time, there have been numerous reports of MIS-C patients across Europe and the United States.<sup>5-29</sup>

Patients with MIS-C are most commonly aged 8-11 years, with a slight predominance of boys, and are normally previously healthy.<sup>7,24,25,28,29</sup> There is typically a delay in

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**Ethics Statement:** The research reported adhered to the relevant ethical guidelines.

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See page 639 for disclosure information.

Every respondent reported use of intravenous immunoglobulin (IVIG), including 53% administering IVIG in all patients. Steroids were most often used for patients with severe clinical presentation or lack of response to IVIG, and only a minority used steroids in all patients (14%). Acetylsalicylic acid was frequently used among respondents (91%), including anti-inflammatory and/or antiplatelet dosing. Respondents reported use of prophylactic anticoagulation, especially in patients at higher risk for venous thromboembolism, and therapeutic anticoagulation, particularly for patients with giant coronary artery aneurysms.

**Conclusions:** There is variation in management of MIS-C patients, with suboptimal evidence to assess superiority of the various treatments; evidence-based gaps in knowledge should be addressed through worldwide collaboration to optimize treatment strategies.

MIS-C presentation after the peak in coronavirus disease 2019 (COVID-19) cases in the local population, by 2-6 weeks, with the current hypothesis that MIS-C is a delayed immune response to a recent SARS-CoV-2 infection rather than direct viral injury.<sup>16,21,24,25</sup> Patients most commonly present with fever, gastrointestinal symptoms, and KD-like symptoms, such as rash and conjunctival injection, along with laboratory evidence of significant inflammation. Presentation varies by age, with younger patients presenting more often with KD-like features, and older patients presenting with more myocarditis-like symptoms, including 73% with myocarditis in the cohort aged 13-20 years, compared to 39% in the cohort aged 0-5 years, in a recent large case series.<sup>24</sup> Cardiac involvement is common, particularly in those with severe presentations, with markedly elevated brain natriuretic peptide levels and mild-moderate troponin elevation.

There have been numerous descriptive case series over the past few months describing clinical presentations of MIS-C. However, data are scarce regarding specific indications for treatment in MIS-C patients, with variation among series. Thus, we surveyed the members of the International Kawasaki Disease Registry (IKDR) to improve our understanding of treatment practices among a large group of pediatric cardiologists.

## Materials and Methods

The IKDR was established in 2013, with the primary objective at inception to study the prevalence of coronary artery aneurysms after KD, along with the clinical and management factors associated with outcomes.<sup>30</sup> Current members of the IKDR include mainly pediatric cardiologists from 65 participating hospitals representing Canada and the United States primarily, with additional sites in Taiwan, Chile, Brazil, Argentina, Mexico, Italy, Australia, Israel, and the United Kingdom. Since the onset of the current pandemic and the emergence of MIS-C, the focus of the IKDR has been directed

**Résultats :** Au total, 56 % des répondants ont déclaré opter pour un traitement immunomodulateur pour tous les patients présentant un SIME, quelles qu'en soient les manifestations. Tous les répondants ont déclaré avoir recours à l'administration d'immunoglobulines par voie intraveineuse, 53 % d'entre eux utilisant ce traitement chez tous les patients. Les stéroïdes étaient plus souvent utilisés chez les patients présentant des symptômes cliniques graves ou ne répondant pas aux immunoglobulines administrées par voie intraveineuse; seule une minorité de répondants ont déclaré utiliser des stéroïdes chez tous les patients (14 %). Les répondants utilisaient aussi fréquemment l'acide acétylsalicylique (91 %), à des doses anti-inflammatoires ou antiplaquettaires. Ils ont en outre déclaré avoir recours à des anticoagulants en prophylaxie, en particulier chez les patients présentant un risque élevé de thromboembolie veineuse, et à une anticoagulothérapie chez les patients présentant des anévrismes coronaires géants.

**Conclusions :** La prise en charge des patients présentant un SIME varie d'un médecin à l'autre, et les données permettant d'évaluer la supériorité des divers traitements employés sont insuffisantes; il conviendrait donc de mettre en place des initiatives de collaboration afin de combler les lacunes des connaissances et d'optimiser les stratégies thérapeutiques.

toward characterizing MIS-C, given the important cardiac manifestations noted in children and the similarities to KD.

We performed an online survey to assess management decisions during hospitalizations for MIS-C. The physicians were asked to identify criteria used for administration of different immunomodulatory and antithrombotic therapies. The 12-question survey was approved by the institutional review board of The Children's Hospital of Philadelphia with exempt determination. The survey was reviewed independently by 3 cardiologists (ME, AD, BM) and underwent a pilot test trial prior to distribution to the IKDR. Responses were anonymous and voluntary, and IKDR members were approached via e-mail and routine virtual meetings with request for completion ([Supplemental Table S1](#)). Only one IKDR member per institution was asked to complete the survey, and answers were collected via the web-based application Research Electronic Data Capture (REDCap) hosted at The Children's Hospital of Philadelphia.

## Results

Among the IKDR membership, members from 36 of 65 institutions completed the survey, with 2 additional members commenting that they have not encountered MIS-C yet, for an overall response rate of 58%.

The most frequently reported specialties treating inpatient and outpatient MIS-C included cardiology (94% inpatient and outpatient), infectious disease (86% inpatient, 47% outpatient), and rheumatology (83% inpatient, 69% outpatient; [Supplemental Figure S1](#)). Additional inpatient providers included general pediatrics (78%), followed by hematology (42%) and immunology (17%).

Among the respondents, 56% reported using immunomodulatory treatment for all MIS-C patients, regardless of presentation. All respondents reported that intravenous immunoglobulin (IVIG) was indicated for MIS-C patients, but the circumstances varied and included the presence of

**Table 1. Case definition of inflammatory syndrome in children**

<i>Royal College of Paediatrics and Child Health, United Kingdom, May 1, 2020</i>	Child presenting with: <ul style="list-style-type: none"> <li>• Persistent fever &gt; 38.5 °C</li> <li>• Laboratory evidence of inflammation (eg: neutrophilia, elevated CRP, lymphopenia)</li> <li>• Single or multi-organ dysfunction</li> <li>• Exclusion of alternative causes</li> <li>• SARS-CoV-2 testing can be positive or negative</li> </ul>
<i>Centers for Disease Control and Prevention, United States, May 14, 2020</i>	Individual aged < 21 y presenting with: <ul style="list-style-type: none"> <li>• Fever (<math>\geq 38</math> °C or subjective) for at least 24 h</li> <li>• Evidence of inflammation (including but not limited to elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes, and low albumin)</li> <li>• Multisystem (<math>\geq 2</math>) organ involvement with evidence of clinically severe illness requiring hospitalization</li> </ul> AND <ul style="list-style-type: none"> <li>• No alternative plausible diagnosis</li> <li>• Positive for current or recent SARS-CoV-2 infection (RT-PCR, serology, or antigen) or exposure within 4 wk prior to symptom onset</li> </ul>
<i>World Health Organization, May 15, 2020</i>	Individual aged $\leq 19$ y with fever $\geq 3$ d AND $\geq 2$ of the following: <ul style="list-style-type: none"> <li>• Rash, bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs</li> <li>• Hypotension or shock</li> <li>• Cardiac involvement (eg: myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, elevated troponin, or elevated NT-proBNP)</li> <li>• Evidence of coagulopathy</li> <li>• Acute gastrointestinal problems</li> </ul> AND <ul style="list-style-type: none"> <li>• Elevated markers of inflammation (eg: ESR, CRP, or procalcitonin)</li> <li>• No other obvious microbial cause of inflammation</li> <li>• Evidence of COVID-19 infection (RT-PCR, antigen test, or serology) or likely contact with patients with COVID-19</li> </ul>

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

clinical features of KD (44%), coronary artery involvement (44%), myocardial involvement (39%), and severe clinical presentation, such as intensive care admission or presentation with shock (39%). Most often, the IVIG dose of 2 g/kg was reported (86%). For 53% of respondents, IVIG was indicated for all MIS-C patients regardless of the presence of additional features (Fig. 1).

Respondents reported steroid use most frequently in patients with severe clinical presentation (64%), followed by those who do not respond to IVIG (ongoing fevers and/or inflammation; 56%; Fig. 1). Only a minority of respondents indicated that they would use steroids for all patients (14%). Other individual responses regarding indications for steroids included the presence of valve dysfunction noted on echocardiogram even without ventricular dysfunction, patients deemed to be at a higher risk of developing coronary artery aneurysms (for example, the very young), and patients with macrophage activation syndrome.

Respondents indicated that they would use adjunct immunomodulatory medications, particularly in severe or refractory cases of MIS-C, including anakinra (58%), infliximab (28%), and tocilizumab (8%). Two additional respondents commented that although they have not encountered a patient with refractory disease yet, they would consider using anakinra or infliximab in that setting.

Acetylsalicylic acid was felt to be indicated by 91% of respondents. Respondents reported anti-inflammatory dosing at 30-50 mg/kg per day (56%), rather than 80-100 mg/kg per day (25%), more frequently, with 17% reporting that they did not use anti-inflammatory dosing. Respondents indicated that anti-inflammatory dosing would be used most commonly for those patients with KD features (53%) and/or coronary artery

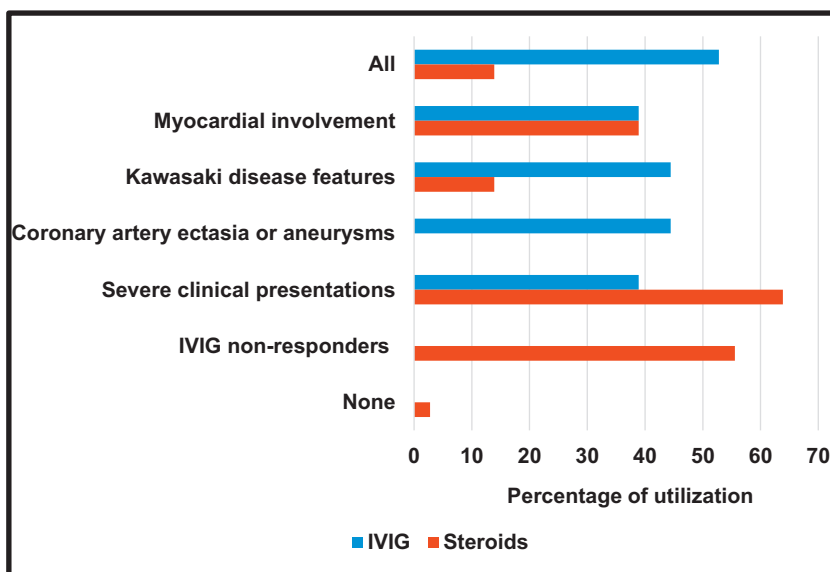
ectasia or aneurysms (50%; Fig. 2). Antiplatelet dosing (3-5 mg/kg per day) would be used most commonly in those with KD features (47%) and coronary artery involvement (39%), but sometimes for all MIS-C patients (33%).

Respondents indicated that they would use prophylactic anticoagulation most commonly for patients felt to have a higher baseline risk for venous thromboembolism, such as the presence of altered mobility and obesity (31% of respondents), in addition to giant coronary artery aneurysms (25%) and elevated D-dimer levels (19%). Therapeutic anticoagulation dosing would be used for patients with giant coronary artery aneurysms (61%) and those with a severe clinical presentation (33%; Fig. 3).

## Discussion

In this survey, we found important variation regarding the management approaches for patients with MIS-C. Approximately half of respondents would treat all MIS-C patients with immunomodulatory therapies, regardless of presentation, whereas others recommended treatment in only severe cases. IVIG was most often indicated, and steroids were typically reserved for more critical cases. Biologic therapies, such as anakinra, were also commonly reported. Respondents frequently used antiplatelet therapy and prophylactic anticoagulation, reserving therapeutic anticoagulation for patients with giant coronary artery aneurysms or severe clinical presentations.

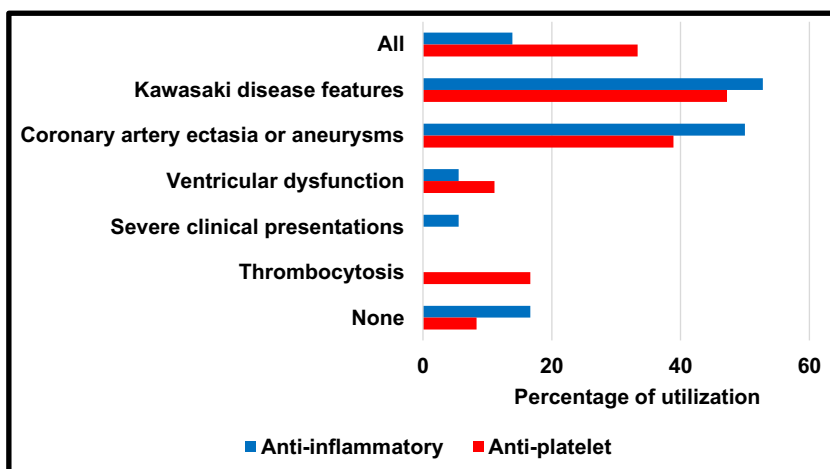
There have been several phenotypes reported in the literature for MIS-C, including (i) severe presentation with shock with or without ventricular dysfunction, (ii) KD-like presentation with evidence of systemic inflammation, and



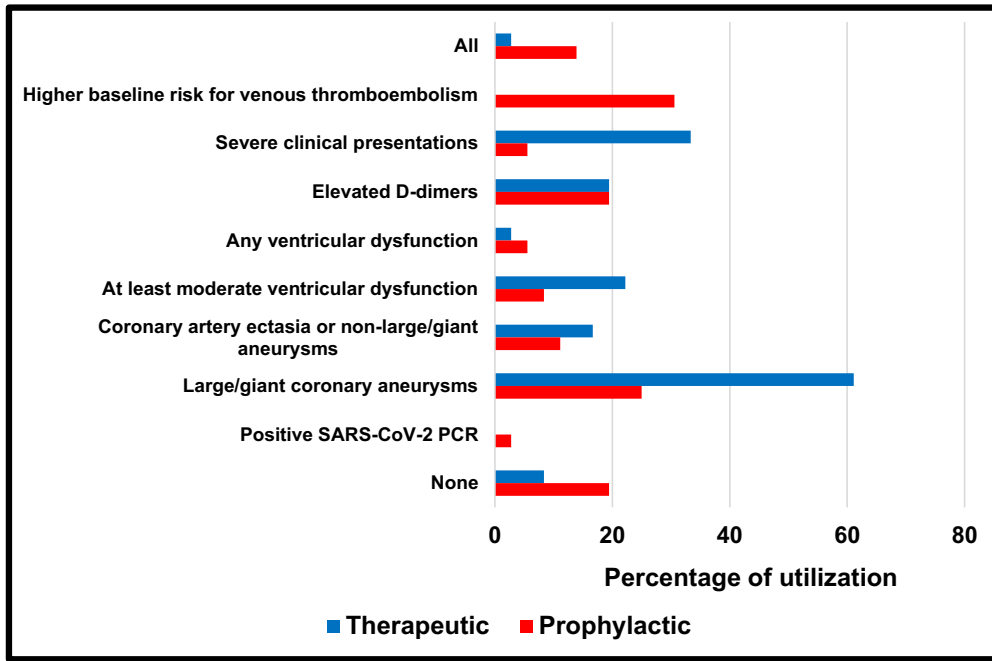
**Figure 1.** IVIG and steroid use in MIS-C among IKDR members. Answer to IKDR survey question regarding indications for IVIG and steroid use in MIS-C patients, based on percentage of responses. Note that survey asked about “coronary artery ectasia or aneurysms” only for IVIG, and about “IVIG non-responders” only for steroids. IKDR, International Kawasaki Disease Registry; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome in children.

(iii) fever with evidence of inflammation not requiring intensive care support (Fig. 4). The degree of shock and hypotension are often out of proportion to the degree of ventricular dysfunction. Some patients have presented with severe ventricular dysfunction with a myocarditis-like presentation; others have had milder ventricular dysfunction without evidence of shock. Ventricular systolic dysfunction is common among MIS-C patients, reported in 33%-55% of patients.<sup>14,24,25,29</sup> Left-ventricular systolic dysfunction has been most commonly in the mild-to-moderately diminished range, although several studies have reported patients with severely diminished ventricular function.<sup>7,25</sup> The presence of coronary artery involvement is less common than ventricular dysfunction, typically found in 8%-19%, but as high as 36%,

of cases.<sup>7,14,24,25,28,29</sup> Although the majority of studies have described mild coronary artery ectasia/aneurysms, the presence of giant coronary artery aneurysms has been reported.<sup>5,14,27</sup> Arrhythmias are not common in MIS-C patients, but they can occur,<sup>5,7,11,13,14,19,23,25</sup> as reported in 12 of 186 patients in one large series.<sup>25</sup> These arrhythmias have included atrial arrhythmias (premature atrial contractions and atrial fibrillation), ventricular arrhythmias (premature ventricular contractions, nonsustained ventricular tachycardia, and one patient with a wide complex tachycardia requiring extracorporeal membrane oxygenation [ECMO]), and atrio-ventricular block (first and second degree without further details on second degree).<sup>14,25</sup> The cardiac presentation of patients with MIS-C is summarized in Table 2.



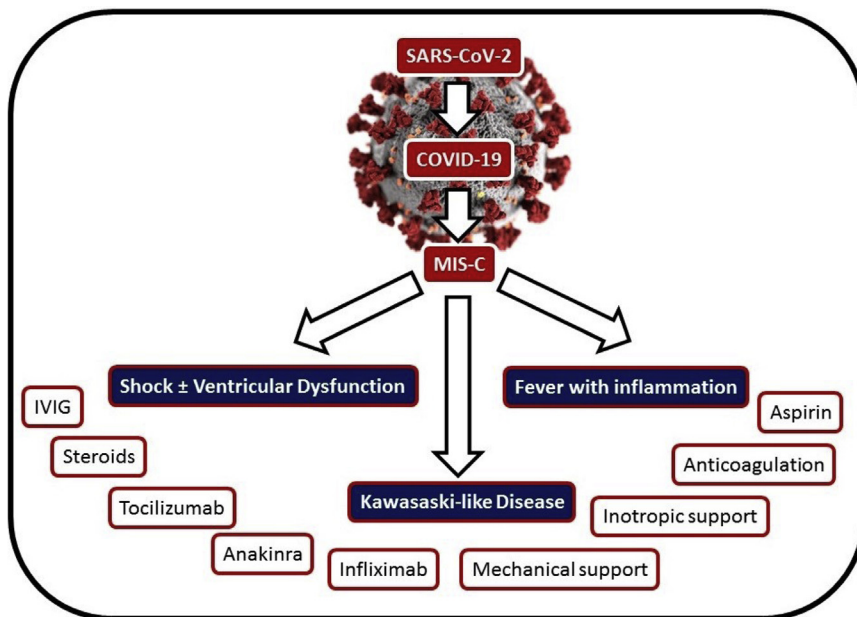
**Figure 2.** ASA use in MIS-C among IKDR members. Answer to IKDR survey question regarding indications for ASA use in MIS-C patients, based on percentage of responses. Note that survey asked about “severe clinical presentations” only for the anti-inflammatory dosing (30-50 mg/kg per day or 80-100 mg/kg per day), and about “thrombocytosis” only for antiplatelet dosing (3-5 mg/kg per day). ASA, acetylsalicylic acid; IKDR, International Kawasaki Disease Registry; MIS-C, multisystem inflammatory syndrome in children.



**Figure 3.** Anticoagulation use in MIS-C among IKDR members. Answer to IKDR survey question regarding indications for anticoagulation use in MIS-C patients, based on percentage of responses. Note that survey asked about “higher baseline risk of venous thromboembolism” only for prophylactic anticoagulation. IKDR, International Kawasaki Disease Registry; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Naturally, given the clinical presentation similar to KD and KD shock syndrome, authors have questioned whether MIS-C is SARS-CoV-2–triggered KD or a distinct entity.<sup>31–35</sup> In Bergamo, Italy, authors compared 19 KD patients prior to the pandemic since 2015—to 10 patients with KD-like presentations in the current era.<sup>6</sup> In addition to the higher

incidence, recent patients have been older, with more frequent cardiac involvement, higher serum ferritin levels, higher neutrophils, lower lymphocytes, lower platelets, and lower sodium levels. Similarly, when comparing 16 MIS-C patients across 7 hospitals in France to patients with KD, MIS-C patients were again older, with similar laboratory differences, increased



**Figure 4.** Clinical presentations of MIS-C. MIS-C patients typically present with shock with or without ventricular dysfunction, Kawasaki-like disease, or fever with inflammation. There are a variety of treatment options, with practice variability. COVID-19, coronavirus disease 2019; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2. Cardiac manifestations in multisystem inflammatory syndrome in children**

	Belhadjer, et al. <sup>7</sup> n = 35 France, Switzerland	Whittaker, et al. <sup>14</sup> n = 58 United Kingdom	Dufort, et al. <sup>24</sup> n = 99 New York, United States	Feldstein, et al. <sup>25</sup> n = 186 United States (excluding New York)
Age (range), y	10 (2-16)	9 (5.7-14)	NP	8.3 (3.3-12.5)
Male gender	18 (51)	25 (43)	53 (54)	115 (62)
Race				
Black	NP	22 (38)	31/78 (40)	46 (25)
Asian	NP	18 (31)	4/78 (5)	NP
White	NP	12 (21)	29/78 (37)	35 (19)
Other	NP	6 (10)	14/78 (18)	107 (58)
Comorbidities	10 (29)	7 (12)	36 (36)	51 (27)
Obese	6 (17), overweight	NP	29 (29)	45/153 (29)
Elevated BNP	28/28 (100)	NP	NP	94/128 (73)
Elevated NT-proBNP	5/5 (100)	24/29 (83)	74/82 (90)	NP
Elevated troponin	35/35 (100)	34/50 (68)	63/89 (71)	77/153 (50)
Echocardiogram findings	n = 35	n = 55	n = 93	n = 170
LV systolic dysfunction	35 (100)	18 (33)	51 (55)	65 (38)
LVEF 30%-55%	25 (71)	NP	NP	56 (33)
LVEF <30%	10 (29)	NP	NP	9 (5)
Pericardial effusion	3 (9)	NP	32 (34)	44 (26)
Coronary artery abnormalities				
Dilation (z score ≥ 2, < 2.5)	6 (17)	1 (2)	NP	NP
Aneurysm (z score ≥ 2.5)	0 (0)	7 (13)	9 (10)	15 (9)
Giant aneurysm (z score ≥ 10)	0 (0)	2 (4)	NP	NP
Arrhythmias	1 (3)	4 (7)	NP	12 (6)
Treatment				
IVIG	25 (71)	41 (71)	69 (70)	144 (77)
Steroids	12 (34)	37 (64)	63 (64)	91 (49)
Inotropic support	28 (80)	27 (47)	61 (62)	90 (48)
ECMO	10 (29)	3 (5)	4 (4)	8 (4)
Mortality	0 (0)	1 (2)	2 (2)	4 (2)

Data are n (%), n/N (%), or median (interquartile range), unless otherwise stated. BNP, B-type natriuretic peptide; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; LV, left ventricle; LVEF, left-ventricular ejection fraction; NP, not provided; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

prevalence of myocarditis, and increased prevalence of IVIG resistance.<sup>17</sup> Whittaker et al.<sup>14</sup> compared the laboratory features for 58 MIS-C children to those from children with KD and KD shock syndrome, based on prior database records from California. The MIS-C patients had consistently different laboratory levels, in addition to older age: higher white blood cells, higher neutrophils, lower lymphocytes, lower hemoglobin, lower platelets, higher C-reactive protein, lower albumin, higher ferritin, higher troponin, and higher D-dimer.<sup>14</sup> Additionally, racial and ethnic backgrounds differ between MIS-C and KD patients. Several studies have commented on the relatively high proportion of MIS-C patients of African-American or Afro-Caribbean descent.<sup>5,11,14,18</sup> There is typically a higher incidence of KD in Asian populations, but authors from South Korea have reported no cases of MIS-C.<sup>36</sup> Lastly, although about 5% of patients with KD present with shock, MIS-C patients present with shock at least 35%-50% of the time.<sup>25,29</sup> Further research, particularly immunologic profiling, is necessary before any conclusions are reached to determine if indeed KD and MIS-C are distinct entities despite their overlapping features.

Management strategies reported in the literature fall into 3 categories: (i) treatment of inflammation, (ii) treatment of shock, and (iii) thromboprophylaxis. However, there is currently suboptimal evidence supporting these treatments among primarily descriptive case series. Fortunately, the vast majority of MIS-C patients have recovered with the current

empiric treatment approaches rather quickly, and among the largest studies across the United States,<sup>29</sup> France,<sup>16</sup> and the United Kingdom,<sup>28</sup> there have been only 13 deaths. These generally positive outcomes increase the difficulty in determining which treatment strategy is the most efficacious.

Management practices for anti-inflammatory treatment for MIS-C have been extrapolated from treatment of KD, toxic shock syndrome, and cytokine storm in COVID-19. Given the overlap of clinical features among KD, myocarditis, and MIS-C, many clinicians have treated MIS-C with IVIG. IVIG has been the mainstay of KD treatment since the 1980s,<sup>37</sup> as recommended by the American Heart Association guidelines,<sup>38</sup> and has sometimes been used in the treatment of myocarditis. Among the largest case series, 70%-81% of patients have received IVIG, with variation in the dose of IVIG used (1 g/kg vs 2 g/kg).<sup>7,24,25,28,29</sup> The use of IVIG varies by presentation, with one series reporting 100% use for those with KD-like presentations, 72% for those with shock, and 61% for those with fever and inflammation alone, although the effect on outcome cannot be determined from these data.<sup>14</sup>

Steroid use, most often methylprednisolone, has been frequently reported in the literature for MIS-C, with a range of 49%-73% of patients receiving steroids across large case series.<sup>24,25,28,29</sup> The rationale for using steroids are its anti-inflammatory properties and frequent use in KD, particularly in high-risk KD patients,<sup>39,40</sup> and other inflammatory disorders. Additional therapies used less commonly in



Treatment of shock
<ul style="list-style-type: none"> <li>• It is reasonable to anticipate that patients with MIS-C may be presenting with ventricular dysfunction. Therefore, consider 10 cc/kg fluid boluses, along with careful reassessments between each administration.</li> <li>• If there is persistent hypotension or evidence of poor perfusion despite fluid resuscitation, consider inotropic support.</li> </ul>
Anti-inflammatory treatment
<ul style="list-style-type: none"> <li>• Patients with mild symptoms, no significant ventricular dysfunction, and no coronary artery involvement may not require any immunomodulatory therapy but would warrant close monitoring.</li> <li>• IVIG should be considered in patients with KD features and/or coronary artery involvement, but it could be considered in all MIS-C patients. Monitor patients closely when administering IVIG due to associated volume load in setting of potential ventricular dysfunction.</li> <li>• Consider addition of steroids in patients with more severe presentations, including those requiring intensive care and/or presenting in shock, and in those who do not respond to IVIG.</li> <li>• Biologic agents, such as anakinra, could be considered as second-line agents.</li> </ul>
Thromboprophylaxis
<ul style="list-style-type: none"> <li>• Refer to the 2017 American Heart Association guidelines for KD when considering antiplatelet and/or anticoagulation therapies in patients with KD features or coronary artery involvement.<sup>38</sup></li> <li>• Low dose aspirin (3-5 mg/kg, maximum 81 mg daily) is reasonable to consider in patients with KD-like presentations and/or coronary artery involvement, with consideration of use in all MIS-C patients.</li> <li>• Consider prophylactic dosing of anticoagulation, such as enoxaparin, in patients at higher baseline risk of venous thromboembolism (ex: patients ≥ 12 years old with altered mobility, obesity, known thrombophilia or history of thrombus, critical presentation, etc.), along with pneumatic sequential compression devices.</li> <li>• Consider therapeutic dosing of anticoagulation in patients with the following: <ul style="list-style-type: none"> <li>• Giant coronary aneurysms</li> <li>• At least moderately diminished ventricular systolic function</li> <li>• Thrombosis concerns</li> </ul> </li> </ul>

**Figure 5.** Best practices for the management of MIS-C, based on literature review and IKDR survey responses. IKDR, International Kawasaki Disease Registry; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children.

the literature for treatment of inflammation include interleukin (IL)-6 inhibitor tocilizumab,<sup>8,10,17,20,21,23,25,27,28</sup> IL-1 inhibitor anakinra,<sup>7,8,10,12,14,20,21,23,25,26,28</sup> and infliximab.<sup>14,20,21,28</sup> Many institutions have used these medications as a second-line agent if there has been no improvement after initial treatment with IVIG, but others have used them for primary treatment, particularly tocilizumab in the presence of cytokine storm.<sup>8</sup>

Patients frequently present with shock, often requiring inotropic support, including epinephrine, norepinephrine, dopamine, dobutamine, and milrinone.<sup>5-28</sup> One particular study commented on the goal of avoiding milrinone due to concern of peripheral vasodilation.<sup>18</sup> The use of ECMO varied considerably as well, with the most prevalent use in France, where 10 of 35 patients with ventricular dysfunction received ECMO support.<sup>7</sup>

Children with MIS-C have laboratory features suggestive of a pro-coagulable state, and the use of antiplatelet and/or

anticoagulation therapies has been reported frequently. Although many studies did not report any acetylsalicylic acid use, others have reported using anti-inflammatory dosing or more commonly antiplatelet dosing.<sup>5,6,9,11,13,15,17,18,20,21,23,28,29</sup> There have only been scattered reports of thrombosis with MIS-C, including 2 patients in the 78-patient United Kingdom study.<sup>28</sup> Several series have discussed anticoagulation,<sup>5,7,12,13,20,21,23,25,28,29</sup> most commonly prophylactic dosing rather than therapeutic dosing. Indications for prophylactic anticoagulation typically were not provided, although one study commented that anticoagulation was indicated for patients with elevated D-dimer or fibrinogen levels, left-ventricular dysfunction, electrocardiographic changes, or any coronary artery abnormality.<sup>21</sup>

The management of MIS-C has been individualized at institutions with various clinical pathways and management algorithms. Recent studies have summarized and sometimes proposed specific therapeutic approaches,<sup>41-46</sup> but there has

not been any study comparing these treatment strategies to assess outcomes. Based on the IKDR survey and review of the literature, we propose best practices for management of MIS-C, which warrants a multidisciplinary approach (Fig. 5).

The IKDR survey regarding management of MIS-C has limitations. We may not have detailed all of the many possible nuances in MIS-C management, but our goal was to assess generally accepted management strategies. The survey may not be reflective of actual practice. The questions asked members about current institutional practices, but members may have responded with approaches they might use in patient scenarios, rather than those actually used. Bias is also possible given that the IKDR members are nearly all pediatric cardiologists, and although practice variation certainly may exist among institutions, there may be variation relative to other providers and IKDR members within the individual institutions as well.

## Conclusions

Treatment of patients with MIS-C often includes management of shock, use of immunomodulatory therapies, and use of thromboprophylaxis agents. Using these approaches, the vast majority of reported patients fortunately have recovered quickly. However, there is wide variation in management, and evidence to assess efficacy and superiority of the various treatment algorithms is suboptimal. Gaps in knowledge should be addressed through prospective trials and registries. Due to the rarity of the condition, multicenter collaboration is critical to understanding of this disease, with the potential for generating increased knowledge regarding KD in the process.

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