




# Multisystem Inflammatory Syndrome in Children and Adolescents (MIS-C) under the Setting of COVID-19: A Review of Clinical Presentation, Workup and Management

Infectious Diseases: Research and Treatment  
Volume 14: 1–12  
© The Author(s) 2021  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/11786337211026642  


Ayesha Farooq<sup>1</sup> , Fatima Alam<sup>1</sup>, Asma Saeed<sup>1</sup>,  
Farooq Butt<sup>2</sup>, Muhammad Azeem Khaliq<sup>1</sup>, Ayesha Malik<sup>3</sup>,  
Manahil Chaudhry<sup>3</sup> and Mohammad Abdullah<sup>1</sup> 

<sup>1</sup>CMH Lahore Medical College and Institute of Dentistry, Lahore, PK-PB, Punjab, Pakistan.

<sup>2</sup>Sialkot Medical College Pvt Ltd, Sialkot, PK-PB Punjab, Pakistan. <sup>3</sup>Hameed Latif Hospital, Lahore, Lahore, PK-PB Punjab, Pakistan.

**ABSTRACT:** Earlier in its course, SARS-CoV-2 was primarily identified to cause an acute respiratory illness in adults, the elderly and immunocompromised, while children were known to be afflicted with milder symptoms. However, since mid-April of 2020, latent effects of the virus have begun emerging in children and adolescents, which is characterised by a multisystem hyperinflammatory state; thus, the term Multisystem Inflammatory Syndrome in Children (MIS-C) was introduced by the WHO and CDC. The syndrome manifests itself approximately 4 weeks after COVID-19 infection, with symptoms mimicking Kawasaki Disease and Kawasaki Disease Shock Syndrome. Demographically, MIS-C peaks in children aged 5 to 14 years, with clusters in Europe, North and Latin America seen, later followed by Asia. Although the exact pathophysiology behind the syndrome is unknown, recent studies have proposed a post-infectious immune aetiology, which explains the increased levels of immunoglobulins seen in affected patients. Patient presentation includes, but is not limited to, persistent fever, rash, gastrointestinal symptoms and cardiac complications including myocarditis. These patients also have raised inflammatory markers including C reactive protein, ferritin and interleukin-6. In poorly controlled patients, the syndrome can lead to multiorgan failure and death. The mainstay of treatment includes the use of intravenous immunoglobulins, steroids, immune modulators and aspirin. Adjunct therapy includes the use of low molecular weight heparin or warfarin for long term anticoagulation. Currently very little is known about the syndrome, highlighting the need for awareness amongst healthcare workers and parents. Moreover, with increased cases of COVID-19 as a result of the second wave, it is essential to keep MIS-C in mind when attending patients with a past history of COVID-19 exposure or infection. Additionally, once these patients have been identified and treated, strict follow-up must be done in order carry out long term studies, and to identify possible sequelae and complications.

**KEYWORDS:** COVID-19, pandemic, multisystem inflammatory syndrome, pediatric, infectious diseases, kawasaki disease, pathophysiology, management, workup

**RECEIVED:** February 4, 2021. **ACCEPTED:** May 30, 2021.

**TYPE:** Review

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**CORRESPONDING AUTHOR:** Ayesha Farooq, CMH Lahore Medical College and Institute of Dentistry, Lahore, PK-PB, Punjab, 54810, Pakistan. Email: aya.apa@gmail.com

## Introduction

Severe Acute Respiratory Syndrome – Coronavirus type 2 (hereby denoted as SARS-CoV-2, or COVID-19) was initially detected in the province of Wuhan, China in December 2019. It spread rapidly throughout the world, and was later declared a pandemic by the World Health Organization (WHO).<sup>1</sup> Following the initial easing up of global lockdowns, the spike in new COVID-19 cases has led to countries reinstating restrictions.<sup>2</sup> It comes as no surprise that COVID-19 has left its mark, not only in terms of infectivity and number of deaths (44.6 million cases and 1.2 million fatalities as of October 30th, 2020),<sup>3</sup> but also in terms of its effect on global markets and economies, as described by the International Monetary Fund (IMF).<sup>4</sup>

In terms of disease burden, the WHO initially described 2 groups of people most susceptible to infection, that is, the elderly and those with underlying health conditions, such as asthma and diabetes, with severity increasing after the age of 40 years.<sup>5</sup> Additionally, it was found that the risk of infection

under the age of 20 is approximately half compared to those over 20 years of age.<sup>6</sup> Thus, there was a general consensus that children (other than infants) were at a lower risk of severe infection.<sup>7</sup>

However, this demographic was questioned once retrospective studies were initiated. One study found that symptomatic COVID-19 infection was less common in children, even though there was a higher incidence of asymptomatic cases when compared to adults.<sup>8</sup> In addition, recent studies have found more sinister findings in children suffering from the disease. A retrospective study in the city of Bergamo, Italy, found a 30-fold increase in the incidence of Kawasaki Disease (KD) following the outbreak of the pandemic. At the same time, these new cases of KD had different epidemiological features compared to classic KD, being seen in older children. Moreover, 50% of children diagnosed with KD fulfilled the criteria for Kawasaki Disease Shock Syndrome (KDSS).<sup>9</sup> Another study in the UK found children with a hyperinflammatory shock syndrome, with similarities to KD and KDSS. These children



also had cardiac complications including coronary artery aneurysms (CAA).<sup>10</sup> Studies carried out in other regions of the world such as the Americas and Asia have supplemented these findings, with a multisystem inflammatory disorder documented in children who were either infected with COVID-19, or were simply exposed to it.<sup>11</sup>

In light of these cases, both the Centre for Disease Control (CDC) and WHO have made preliminary case definitions for the term Multisystem Inflammatory Disorder in Children and Adolescents (MIS-C), associated with COVID-19 infection.<sup>12,13</sup> While the criteria overlap significantly with that of KD, atypical KD and Toxic Shock Syndrome (TSS),<sup>11</sup> there are also distinct differences. Some these have been displayed in Table 1.

Developing an understanding of the impact of COVID-19 on the paediatric and adolescent population is of prime importance, especially considering how the findings of recent studies are now opposing those carried out earlier in the pandemic. As the signs of MIS-C seem benign at first, like diarrhoea, vomiting, fever and rash, it is necessary that they are given their due importance and considered red flags. This is especially true in patients who report a past history of COVID-19 infection or exposure. The chronology of these symptoms must also be taken into consideration, given the proposed post-infectious nature of the syndrome, with a high index of suspicion in cases presenting approximately 1 month after having COVID-19.<sup>11</sup>

Given that the spike in new COVID-19 cases is rampant, it is plausible to consider a second spike in MIS-C cases. It is therefore imperative that not only specialists, such as paediatricians and cardiologists be made aware of MIS-C, other healthcare workers should also include this syndrome in their differential diagnosis. Moreover, as it affects children and adolescents, public health campaigns are needed to make parents aware of the possible sequelae following COVID-19 infection.

The aim of this review article is not only to summarise current data available on MIS-C, but also to provide a comprehensive work-up and management plan for dealing with a patient suffering from the syndrome.

## Methodology

An independent review team was made to minimise bias, who identified relevant articles from PubMed, Google Scholar, Wiley Online Library, Medscape and Science Direct. The following search terms were used for identifying articles: 'coronavirus', 'multi-inflammatory syndrome', 'hyperinflammatory state', 'MIS-C', 'Kawasaki disease', 'epidemiology', 'clinical presentation', 'laboratory diagnosis', 'treatment', 'clinical trials', 'immune modulators', 'workup', 'pathophysiology' and 'immunopathogenesis'. In addition to research articles, the team also investigated data from the websites of organisations including the CDC and WHO. Relevant information was also extracted from news websites such as the British Broadcasting Channel

(BBC), and from hospital websites like the Children's Hospital of Philadelphia (CHOP) and Health Service Executive (HSE).

The literature for this article was reviewed over a period of 2 months, from 15th August 2020 to 15th October 2020. As data on MIS-C is ever-emerging, a member of the review team continued searching for relevant studies until the final manuscript was completed, in order to ensure all literature was up-to date.

The aim of the review team was to include full length articles in the English language. Studies published in 2020 were preferred due to their relevance. Articles containing definitions for MIS-C were shortlisted, in addition to studies focusing on epidemiology, differences between MIS-C and KD, pathophysiology, workup and treatment. Case studies were also included in literature, with a focus on those articles which initially documented a KD-like illness after the outbreak of COVID-19.

The data collected was then handed over to the most experienced member of the review team for evaluation. Five papers were excluded as their full text was unavailable, and a further 6 were disregarded on the basis of irrelevant information. A total of 62 texts were included in the review.

## Review

### *Epidemiology*

The phenomenon of MIS-C was initially documented in Europe and North America, although cases in other parts of the world have also begun emerging. Ethnicities majorly affected include those of African or Afro-Caribbean descent, as well as Hispanics/Latinos. This is in contrast to KD, which is typically prevalent in East Asia.<sup>10,14,15</sup>

Older children are more commonly affected, with peak incidences in 5 to 14 year olds, with slightly higher male preponderance.<sup>15</sup> According to the WHO, the cut-off age is 19 years,<sup>13</sup> while the CDC accommodates up to the age of 21.<sup>12</sup> Contrastingly, KD occurs more commonly in children less than 5 years.<sup>16</sup>

Furthermore, it is important to note that the incidence of MIS-C, although associated with COVID-19 infection, does not peak at the same time as COVID-19 does. Studies have found there to be a gap of 4 weeks in between increased cases of COVID-19 and MIS-C.<sup>11</sup>

### *Pathophysiology*

In order to understand the pathophysiology of MIS-C, it is important to examine the structure and mechanisms of the SARS-CoV-2 virus. The coronavirus is a single stranded RNA virus, divided into 4 genera, namely;  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ .<sup>17</sup> The  $\beta$  genus incorporates the SARS-CoV-2 virus, and is also responsible for the previous outbreak of SARS and the Middle East Respiratory Syndrome (MERS).<sup>18</sup>

**Table 1.** Definitions and key differences between MIS-C (CDC), MIS-C (WHO), KD and atypical KD.

	MIS-C	MIS-C	MIS-C	KAWASAKI DISEASE	ATYPICAL/INCOMPLETE KAWASAKI
Body	CDC	WHO	WHO	CDC	CDC
Age	<21 years	0-19	0-19	Not specified	Not specified
Fever status	Fever ≥38.0°C for ≥24 h, or report of subjective fever lasting ≥24h	Fever ≥3 days	Fever ≥3 days	Fever ≥5 days	Fever ≥5 days
Diagnostic criteria	Fever, laboratory evidence of inflammation, evidence of clinically severe illness requiring hospitalisation with multisystem involvement (≥2 organ systems: cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic, or neurological)	Fever and 2 of the following: (i) Rash or bilateral non-purulent conjunctivitis or signs on muco-cutaneous inflammation (oral, hands or feet) (ii) Hypotension or shock (iii) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated TnT/NT-proBNP) (iv) Evidence of coagulopathy (by PT, PTT, elevated D-dimers) (v) Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	(i) Rash or bilateral non-purulent conjunctivitis or signs on muco-cutaneous inflammation (oral, hands or feet) (ii) Hypotension or shock (iii) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated TnT/NT-proBNP) (iv) Evidence of coagulopathy (by PT, PTT, elevated D-dimers) (v) Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	At least 4 of the following 5: (i) rash (ii) cervical lymphadenopathy (at least 1.5 cm in diameter) (iii) bilateral conjunctival infection (iv) oral mucosal changes (v) peripheral extremity changes	Illness does not meet case definition, but patients have fever and coronary artery abnormalities
Inflammatory markers	Including (but not limited to) 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin	Elevated markers of inflammation such as ESR, CRP or procalcitonin			
Exclusion criteria	No alternative diagnosis	No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes			
Blood culture	Negative	Negative		Negative	Negative
COVID-19 status	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within 4 weeks prior to symptoms	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19			

Sources: Jiang et al.,<sup>11</sup> CDC,<sup>12</sup> Freedman et al.<sup>13</sup>  
 Abbreviations: COVID-19, coronavirus disease; CRP, C-reactive protein; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus type 2; TnT, troponin T.

Of the structural proteins present on the virus's surface, the spike protein is of prime importance, being responsible for viral entry into cells, via its S1 and S2 subunits. Additionally, it is these subunits that have shown to adapt and diversify over time, learning to evade the body's immune system.<sup>17</sup> Moreover, the receptor binding domain (RBD) of the spike protein has shown to have affinity for angiotensin converting enzyme 2 (ACE2), which can be found in the following organ tissues: small and large intestines, kidneys, lungs, vascular endothelium and testis. Their abundance in type I and II alveolar epithelial cells account for the virus's strong affinity for invading lung tissue.<sup>19</sup> Upon entry into the host cell, the virus begins to replicate by attaching to host ribosomes and initiating protein synthesis. The virions are then packaged in the Golgi apparatus, and later released out of the host cell.<sup>20</sup>

Infection with the SARS-CoV-2 virus also causes the release of a number of cytokines. Dendritic cells (DCs) in the lung parenchyma act as antigen presenting cells (APCs), thus triggering the release of cytokines such as interferons (IFN), interleukins (IL), tumour necrosis factor (TNF) and inflammatory chemokines. Afflicted alveolar macrophages and airway epithelial cells (AEC) also assist DCs in the formation of cytokines, however to a lesser extent.<sup>21</sup> Of these mediators, IL-6, carries particular importance as it regulates the acute phase response, as well as activating T helper 17 (TH17) cells as part of the DC response. Moreover, studies have also shown there to be a positive correlation between IL-6 levels and disease severity.<sup>22</sup> These cytokines (IL-1, IL-6 and TNF- $\alpha$ ) are also notoriously known to cause fever.<sup>23</sup> Finally, T killer cells are activated from naïve T cells; however, their responses have been shown to differ with disease intensity. In cases of mild disease, T killer cells under the influence of IL-2, IFN-I and IFN-III undergo activation and clonal expansion. On the other hand, in severe disease states, increased levels of IL-6, IL-10 and TNF have been shown to reduce levels of circulating T killer cells, contributing to the lymphopenic state seen in severely affected patients.<sup>24</sup> Individually, these factors play a role in mediating the hyperinflammatory state seen in some patients with COVID-19, while together they combine to encompass the cytokine storm, which is a key element in the development of MIS-C.<sup>25</sup>

Additionally, the immunopathogenesis of MIS-C can be linked back to the spike protein. Some studies have suggested its behaviour as a super-antigen, similar to that of the enterotoxin of *Staphylococcus aureus*, which could in turn activate the cytokine storm, leading to a hyperinflammatory state.<sup>25</sup>

The body's humoral response also plays a key role in the development of MIS-C. Children afflicted with MIS-C were found to have elevated levels of immunoglobulin G (IgG) in their blood, which was indicative of past infection, supporting the idea that MIS-C is a post-infectious phenomenon,<sup>11,26</sup> A recent study found increased levels of IgG, IgA and IgM titres specifically against spike protein several weeks following discharge. Additionally, auto-antibodies were seen in these

patients which reacted not only to IgG and IgA, but also against anti-La and Jo-1, which opens the door for comparisons with other autoimmune conditions like Sjogren's syndrome. When further examined, these auto-antigens were found abundantly in areas classically affected by MIS-C, including cardiac tissue and intestines.<sup>27</sup>

In summary, the pathogenesis of MIS-C can be described as 2-fold: (i) cell mediated and (ii) humoral mediated. APCs present antigens to undifferentiated T cells, which then undergo activation and carry out a number of functions including T killer cell mediated cell death and T helper cell mediated cytokine release, resulting in the cytokine storm. Additionally, spike proteins on the viral surface act as super antigens, exaggerating the host immune response. Antibodies are formed against viral antigens causing the formation of immune complexes. Moreover, autoantibodies are also formed against IgA and IgG, all together causing a multisystemic inflammatory state.

MIS-C acts on a wide spectrum, affecting a multitude of organ systems. Individually, its affects are as follows.

### Cardiovascular System

The entry of the virus into cardiac tissue and the release of cytokines results in not only endothelial injury, but also direct myocardial injury. Endothelial injury has traditionally been recognised by raised levels of von Willebrand factor (vWF) in the bloodstream; however, a recent study has pointed towards soluble thrombomodulin being not only a marker of endothelial damage, but also a prognostic indicator.<sup>28</sup> On the other hand, myocardial damage is characterised by a number of findings such as increased Troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in these patients. Endothelial injury can lead to the formation of CAAs, while direct myocardial injury can cause myocarditis,<sup>29</sup> as documented in MIS-C patients. Many of these features correlate strongly with KD, in which CAAs in the young are characteristic.<sup>9</sup>

The pathogenesis of shock in these patients can also be linked to the cytokine storm. A study by the American Heart Association (AHA) found that patients suffering from acute heart failure in the setting of MIS-C had raised inflammatory markers such as IL-6. Additionally, these patients suffered from left ventricular (LV) dysfunction (one-third of patients had an ejection fraction (EF) <30%), thus requiring inotropic support. However, myocardial stunning and/or oedema was noted to be the probable cause of LV dysfunction, as opposed to myocarditis.<sup>30</sup>

### Gastrointestinal System and Liver Injury

A meta-analysis by The Lancet<sup>31</sup> found that 15% of patients with COVID-19 had gastrointestinal symptoms, while 19% of patients had evidence of liver injury, highlighting the commonality of these complications.

The oesophagus and small intestine, in particular its proximal and distal enterocytes, have large numbers of ACE2 receptors on their cell surface. It is therefore these cells that are

preferentially affected. Moreover, ACE2 is known for playing a role in gut homeostasis, including enzyme regulation and amino acid uptake. Studies on mice have found inflammatory changes and colitis in subjects with altered ACE2. As a result, diarrhoea is a common symptom in patients with COVID-19, and in-turn, MIS-C.<sup>32,33</sup> On the other hand, liver injury can be due to a number of reasons, including direct viral injury, as well as secondary injury due to the inflammatory response, and drug toxicities. It is characterised by mildly raised hepatic enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT).<sup>31</sup>

### Haematological Manifestations

Lymphopenia is a characteristic of COVID-19 which becomes evident approximately 1 to 2 weeks after the onset of symptoms. Its exact pathogenesis is unknown, with theories including ACE2 mediated viral entry into lymphocytes causing cell death, as well as secondary apoptosis due to the cytokine storm, and the release of TNF- $\alpha$ . Lymphoid tissue such as the spleen and lymph nodes can also be similarly affected.<sup>34</sup> Hypercoagulability is also a salient feature of both COVID-19 and MIS-C, with studies showing patients having increased D-dimers and prolonged prothrombin time (PT). Moreover, thrombocytopenia is also a common finding, although as it was 'mild' in 70% to 95% of patients with severe COVID-19 infection, it is not a strong predictor of disease outcome. Together, this combination of raised D-dimers, prolonged PT and decreased platelet count, portray a picture similar to disseminated intravascular coagulation (DIC). Additionally, post-mortem studies have revealed thrombotic microangiopathies in the lungs of affected patients. Thus, there is a combination of DIC and thrombosis, putting patients at risk of thromboembolic events, especially in the setting of immobility.<sup>11,35</sup>

### Dermatological Manifestations

Multiple cases of COVID-19 have presented with rash. Children have reported with erythematous-to-violaceous rashes and chilblain-like lesions on the dorsal surfaces of their hands and feet. It is also interesting to note that these were their presenting findings, and polymerase chain reaction (PCR) sampling was done based on a history of COVID-19 exposure.<sup>36</sup> The pathophysiology of these findings is not clearly understood; however, some studies have pointed towards complement mediated microvascular thrombotic injury as a potential cause, due to the discovery of C5b-9, C3d and C4d deposition in the micro-vessels in affected patients.<sup>37</sup>

### Renal Involvement

Cells of the kidney, including proximal and distal tubular cells, as well as podocytes, contain ACE2 receptors<sup>19</sup> making them a target for viral entry, which initiates destructive processes leading to Acute Kidney Injury (AKI). This can be due to viral mediated cell death causing acute tubular necrosis (ATN), or as a result of decreased renal perfusion secondary to the cytokine storm and shock.<sup>38</sup>

### Nervous System Involvement

The effects of SARS-CoV-2 on the nervous system are multi-tude. ACE2 receptors present in neuronal tissues can help account for neurological symptoms, including hyposmia, anosmia and ageusia. Studies on mice have shown high concentrations of the virus in the olfactory bulb, as well as the basal ganglia and midbrain.<sup>39</sup> Alternative mechanisms of injury have also been proposed, including the interplay between humoral immune responses and the cytokine storm, as well secondary injury due to hypoxia and hypotension. As a result of hypercoagulability, micro-thromboses also occur in these patients, leading to neuronal injury, manifesting on a spectrum of confusion and headaches, to overt encephalopathy, seizures and delirium. Additionally, post mortems of these patients have revealed neuronal hyperemia, oedema and degeneration.<sup>40,41</sup>

### Respiratory System

The entry of the virus into pneumocytes causes alveolar cell injury, activation of macrophages and the release of cytokines, such as TNF- $\alpha$ , IFN, IL-6 and IL-8; together these can cause a state of severe lung inflammation. However, severe respiratory symptoms are less common in MIS-C, as it develops after COVID-19 subsides.<sup>11,21</sup>

A summary of the findings in MIS-C patients have been elucidated in Figure 1.

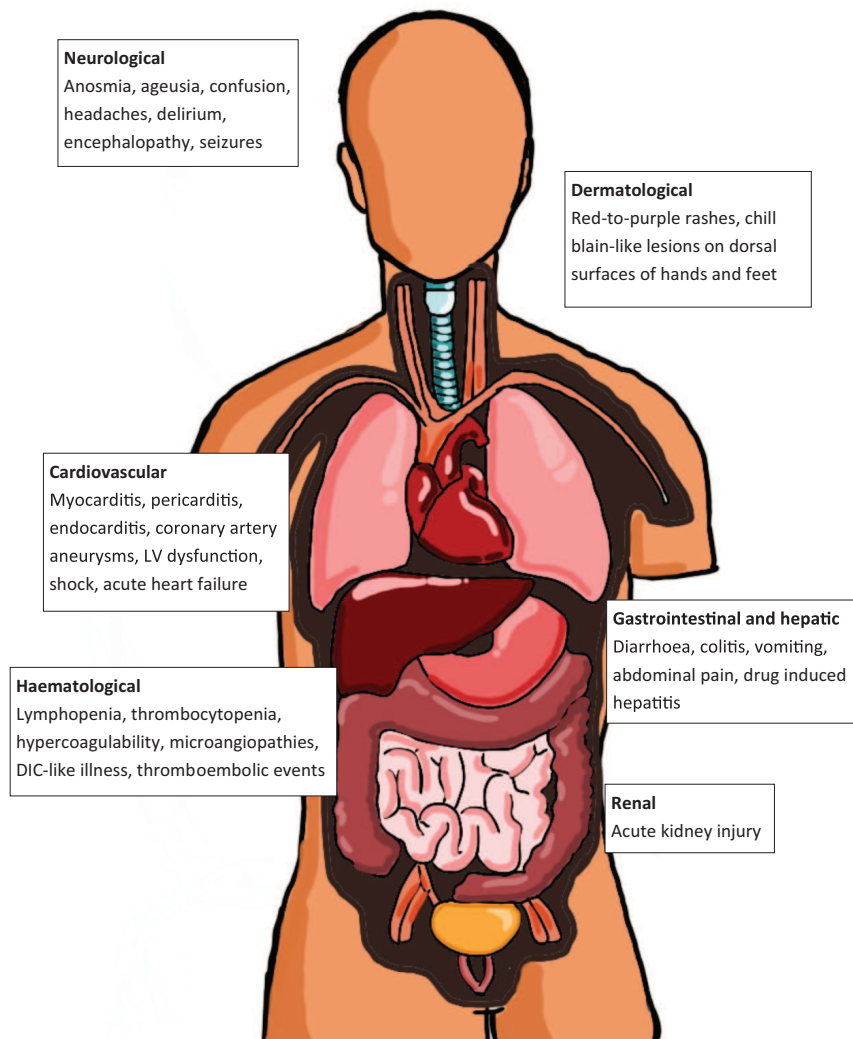
### Workup

The workup for MIS-C is dependent on its timely diagnosis. Definitions for the syndrome have been described by both the WHO and CDC, as mentioned earlier, and the criteria should be addressed at the patient's first visit.

Following the diagnosis of MIS-C, it is important to carry out certain immediate tests in the emergency department. In cases of vitally stable patients suspected of having MIS-C, CHOP has recommended the following blood tests: complete blood picture (CBC), complete metabolic profile (CMP), C-reaction protein (CRP) and erythrocyte sedimentation rate (ESR). It is on the basis of these preliminary tests that the further course of management is decided. On the other hand, in patients who are vitally unstable and suspected of having MIS-C, resuscitation carries primary importance, with the use of volume expanders and vasopressors in shock-like states.<sup>42</sup>

In case of deranged reports, it is suggested to carry out further testing, which includes amongst others, the collection of nasopharyngeal samples for the PCR of SARS-CoV-2.<sup>42</sup> Upon isolation and admission to the ward for stable and intensive care unit (ICU) for unstable patients, it is recommended that a full workup be done, in coordination with a multidisciplinary team (MDT), consisting of immunologists, cardiologists, rheumatologists, infections disease specialists and intensivists.<sup>11</sup>

The workup in ward can be divided 3-fold; blood tests, fluid analysis and imaging studies. For blood tests, the following are recommended<sup>26,43</sup>:



**Figure 1.** Pathological findings in MIS-C patients.

Abbreviations: DIC, disseminated intravascular coagulation; LV, left ventricular.<sup>28-41</sup>

- CBC with differential
- Renal function tests (RFT)
- Liver function tests (LFT)
- Blood gases
- Cardiac markers: TnT, creatinine kinase (CK-MB), lactate dehydrogenase (LDH), pro-BNP
- Coagulation profile: PT, partial thromboplastin time (PTT), international normalised ratio (INR), D-dimers, fibrinogen
- Inflammatory markers: CRP, ESR, IL-6, procalcitonin, ferritin
- Blood culture

It is important to note here that blood cultures while negative for MIS-C and KD, will be positive for TSS, which is its major differentiating point.<sup>11</sup>

Fluid analysis consist of urinalysis and culture, as well as stool analysis and culture in case of relevant symptoms such as

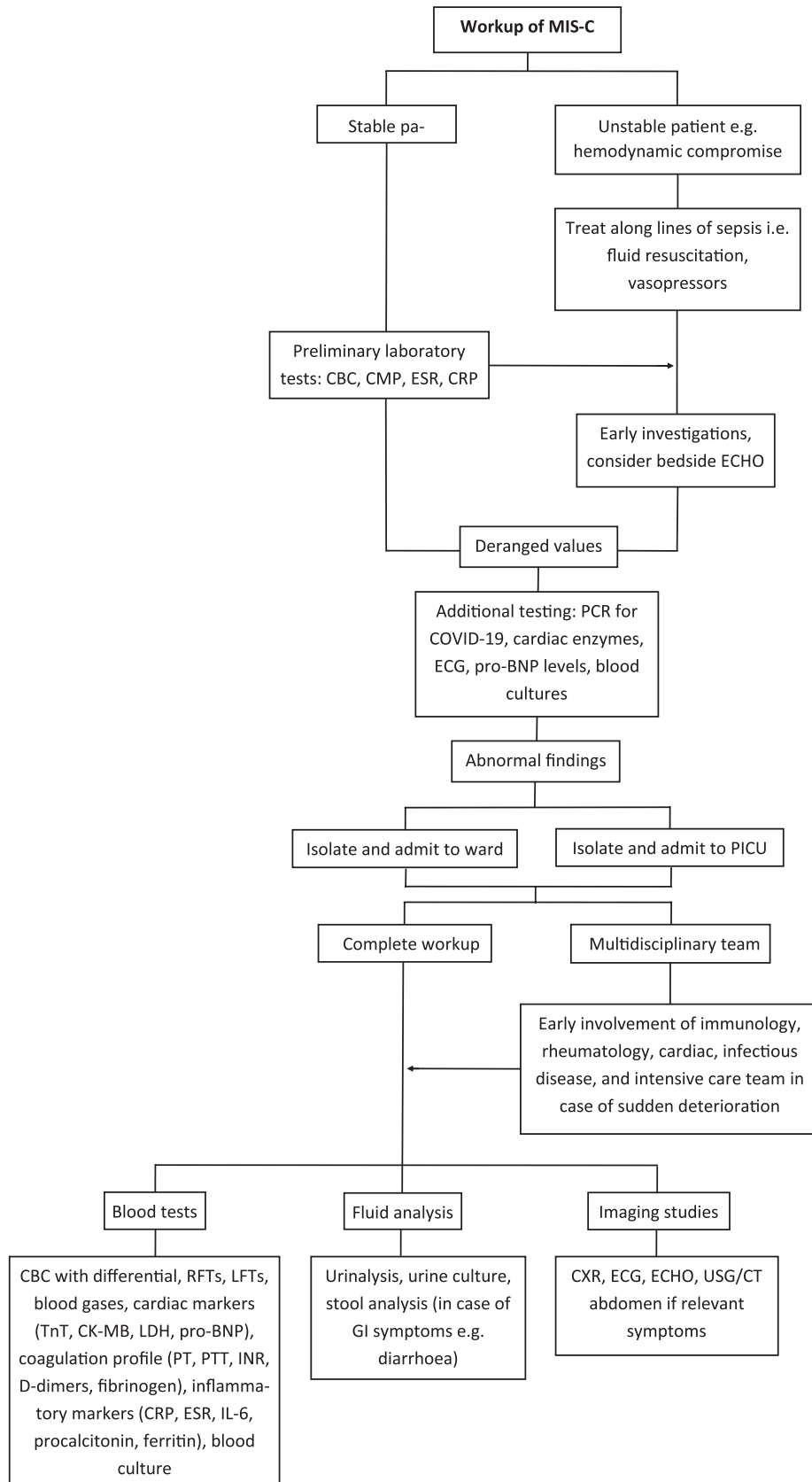
burning micturition or diarrhoea.<sup>43</sup> Imaging studies comprise of chest x-rays, which may reveal ground glass opacities and patches of consolidation in COVID-19 positive patients.<sup>44</sup>

Additionally, electrocardiography (ECG) and echocardiography (ECHO) comprise of essential investigations, due to the prevalence of cardiac complications in these patients.<sup>10</sup> Adjunct investigations include ultrasonography (USG) and computed tomography (CT) abdomen, which should only be done in cases where physical findings/history warrant further investigations.<sup>43</sup>

A comprehensive model incorporating the aforementioned has been shown below in the Figure 2.

### Treatment

As with the workup of MIS-C, its management also requires an MDT, with the involvement of specialists relevant to the patients' presentation, which may include paediatric cardiologists, rheumatologists, immunologists and intensivists.<sup>10,11</sup>



**Figure 2.** Workup for MIS-C patients. Abbreviations: CBC, complete blood count; CK-MB, creatinine kinase-MB; CMP, complete metabolic profile; CRP, C-reactive protein; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiography; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IL-6, interleukin 6; INR, international normalised ratio; LDH, lactate dehydrogenase; LFT, liver function tests; PCR, polymerase chain reaction; pro-BNP, pro-brain natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RFT, renal function tests; TnT, troponin T; USG, ultrasonography.<sup>11,26,42-44</sup>

Similar to KD, the mainstay of treatment for stable patients with MIS-C entails the use of aspirin and intravenous immunoglobulins (IVIG), which has resulted in complete recovery in a number of cases.<sup>10,26</sup>

A general consensus for the treatment of MIS-C comprise of a combination of (IVIG), steroids, immune modulators and aspirin.<sup>26,45-49</sup>

### Intravenous Immunoglobulins (IVIG)

Similar to KD, IVIG use is strongly recommended in MIS-C patients; however, its exact mechanism of action is not clearly understood. Nevertheless, IVIG therapy has shown to have anti-inflammatory effects in MIS-C patients, with significant reductions in inflammatory markers seen post-infusion.<sup>30</sup> It is also of note that recent studies have shown IVIG to be beneficial in the management of myocarditis secondary to COVID-19, highlighting the therapeutic range of the drug.<sup>50</sup>

Prior to initiating therapy, the patient's cardiac status must be assessed. If anomalous, IVIG infusion should be delayed. The recommended dose of IVIG is 1 to 2g/kg in stable patients, though in cases resembling KDSS, raised CRP (>130g/dL), Asian race, admission ECHO with z-score >2.5 or presence of CAA, the dose can be increased to 2g/kg as a single infusion, while concomitantly administering a 3-day pulse of intravenous (IV) prednisolone.<sup>49,50</sup>

### Shock, Steroid Use and Respiratory Support

Patients suffering from shock benefit from fluid resuscitation, steroid use, invasive monitoring, vasopressors, intubation and mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) is known to be beneficial in patients suffering from severe cytokine storm, cardiogenic or septic shock.<sup>49</sup>

High dose IV pulse of corticosteroids for 3 days have been recommended in shock-like states, along with a single infusion of IVIG at 2g/kg.<sup>49</sup> Additionally, steroids have been found to be particularly useful in patients suffering from cardiac abnormalities, such as LV dysfunction.<sup>30</sup> However, it is imperative that in such cases, fluid overload be strictly avoided.<sup>51</sup> The dose of steroids increases according to disease severity, with one study recommending a range of 2 to 30 mg/kg/day of methylprednisolone, with higher doses suggested in sicker patients. Inotropic agents are also useful in patients suffering from shock secondary to myocardial dysfunction, and include drugs such as epinephrine and dobutamine.<sup>47</sup>

Mechanical ventilation can be useful in patients requiring respiratory support.<sup>52</sup> Despite appropriate medical therapy, it is noteworthy that patients can progress to respiratory or cardiac failure, requiring the need for intubation and use of ECMO.<sup>53</sup>

### Aspirin and Therapeutic Anticoagulation

Aspirin has a key role in the therapeutic anticoagulation of these patients. It is necessary that patients' risk of thrombosis be assessed and management be tailored accordingly.<sup>50</sup> This is especially true in patients with raised inflammatory markers,

D-dimers and fibrinogen. It is recommended that drug choice and doses be carefully evaluated with guidance from paediatric haematologists.<sup>11</sup>

It is suggested that low dose aspirin (3-5 mg/kg/day, not exceeding 81 mg/day) be given to patients with MIS-C with or without thrombosis (platelet count  $\geq$  450 000/ $\mu$ L). This should be continued until platelet count normalises or normal coronary arteries are seen at least 4 weeks after diagnosis.<sup>11,50</sup>

Other studies recommend an increased aspirin dose of 20 to 25 mg/kg every 6 hours (equating to 80-100 mg/kg/day) be given to patients with raised inflammatory markers (ferritin > 700 mg/mL or CRP > 30 g/dL), or cardiac involvement. The dose can later be tapered once the patient has been afebrile for  $\geq$ 24 hours, returning to 3 to 5 mg/kg as a single daily dose.<sup>49</sup>

Additionally, patients presenting with CAAs, or raised D-dimers and fibrinogen are recommended to have low molecular weight heparin (LMWH) such as enoxaparin, or warfarin be added to their treatment regimen.<sup>50,54</sup>

The z-score of CAAs should be calculated as they carry therapeutic significance; a maximal score of 2.5 to 10.0 warrants treatment with aspirin only. However, in cases where the z-score is  $\geq$ 10.0, a combination of low dose aspirin and an anticoagulant such as enoxaparin or warfarin is recommended. These drugs should be continued for at least 2 weeks following discharge if the patient suffered from thrombosis or had an EF <35%.<sup>50</sup>

However, a discussion on aspirin is incomplete without mention of its limitations. Newer studies are bringing into question the efficacy of aspirin use in children, taking into consideration their risk of developing Reye Syndrome. It is important to note that aspirin – while effective in reducing the febrile stage of KD – does not appear to play a role in reducing the incidence of cardiac complications like CAAs.<sup>55,56</sup>

### Immune Modulators/Biological Agents

Patients with increased levels of pro-inflammatory cytokines including IL-1, IL-6 and TNF- $\alpha$  have shown to have stunted responses to IVIG, aspirin and steroid therapy.<sup>10,11,26</sup> Therefore, it is necessary to include immune modulating drugs in treatment regimens. These include anakinra (IL-1 receptor blocker), tocilizumab (IL-6 inhibitor) and infliximab (anti-TNF- $\alpha$ ).<sup>11,47</sup>

The recommended dose of anakinra is 2 to 10 mg/kg/day, which can be administered subcutaneously or IV, and is given in divided doses every 6 to 12 hours.<sup>50,54</sup> Its use not only decreases the need for invasive ventilation, but also reduces mortality. Moreover, as it has a quick onset and short half-life, patients' response to therapy can be assessed early, allowing physicians to explore other treatment options if need be.<sup>49,57</sup> However, administration of this drug requires regular monitoring of LFTs as the drug is hepatotoxic in nature.<sup>50,58</sup>

Tocilizumab, a monoclonal antibody targeting IL-6, has garnered a substantial amount of attention during the pandemic, being administered in patients with severe pneumonia in order to decrease their risk of invasive mechanical ventilation.<sup>57</sup> However, the use of this drug is still undergoing clinical



trials, and has not yet been approved for standardised treatment against COVID-19.<sup>59</sup> Criteria for its use have been made by a number of bodies. The HSE recommend the use of tocilizumab in patients with suspected hyperinflammation in COVID-19 if they fulfil all of the following prerequisites<sup>60</sup>:

1. Consideration of treatment after joint approval in a multidisciplinary team, preferentially in an ethically approved clinical trial if possible
2. Confirmed COVID-19 pneumonia on X-ray/CT and at least one of the following:  $\text{SaO}_2 \leq 93\%$  and/or  $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$
3. Established hyperinflammatory state, that is, significantly raised markers of inflammation including CRP, D-dimers and ferritin, which correlate with increased IL-6 levels in these patients
4. Exclude any other infectious cause

When administered, its single dose is calculated by weight; 12 mg/kg IV if  $< 30 \text{ kg}$ , and 8 mg/kg IV if  $> 30 \text{ kg}$ , with the maximum dose being 800 mg.<sup>50</sup>

In order to assess response to therapy, serial monitoring of inflammatory markers is recommended (ferritin, CRP, fibrinogen, D-dimers). IL-6 levels should also be monitored if possible. Additionally, procalcitonin levels are useful in ruling out bacterial superinfections. The adverse effects of tocilizumab include the acquisition of bacterial, fungal and opportunistic infections, as well as tuberculosis, along with causing liver injury.<sup>50,60</sup>

Infliximab is a TNF- $\alpha$  inhibitor, classically used in chronic inflammatory disorders.<sup>61</sup> One case study examined the effect of infliximab on a paediatric patient suffering from both MIS-C and Crohn's disease. As both involve the release of a myriad of inflammatory factors, infliximab was chosen as an ideal combating agent. Two doses were given: the first on day 8 of symptoms at a dose of 10 mg/kg IV, which resulted in resolution of fever, tachycardia and hypotension on the same day. The next dose was given 5 days later with the same strength. It is also interesting to note that TNF- $\alpha$  levels dropped from 97.8 pg/mL to 9.1 pg/mL following the first infusion (reference range 0–22 pg/mL).<sup>62</sup> Other studies have similarly documented the incorporation of infliximab in treatment regimens of MIS-C patients.<sup>11</sup>

### Role of Antibiotics and Antiviral Therapy

As the symptoms of MIS-C overlap those of severe bacterial infections, it is recommended that broad spectrum antibiotics be added at the time of admission, and discontinued once bacterial causes have been ruled out/cultures become negative after 48 hours of admission.<sup>10,11,49,54</sup>

While some studies used a combination of vancomycin, clindamycin and ceftriaxone as initial management,<sup>53</sup> ceftriaxone alone is also sufficient in cases of mild illness. Additionally, metronidazole is recommended for use in patients with predominant gastrointestinal symptoms. However, in shock-like

states, drug combinations are advised. One study suggested combinations of vancomycin, clindamycin and cefipime, or vancomycin, meropenem and gentamicin.<sup>49</sup>

The role of antiviral agents in patients with MIS-C is questionable. This is primarily due to the proposed post-infectious pathogenesis of the syndrome, which entails the lack of active viral replication.<sup>11</sup> Nevertheless, they can be given in patients who are PCR positive. The current drug being tested is remdesivir, which is given to children intravenously, at an initial loading dose of 5 mg/kg (maximum 200 mg) on day 1, followed by 2.5 mg/kg (100 mg maximum dose) daily for 9 days.<sup>49</sup>

### Discharge Criteria

The general criteria for discharging MIS-C patients is based on disease severity and clinical status. However, the following can be included: lack of fever for 48 hours after discontinuing antipyretics (except steroids), improvement of clinical symptoms such as rash and diarrhoea, and/or normalisation of laboratory markers.<sup>48</sup> Additionally, patients must be off supplemental oxygen.<sup>11</sup>

One study suggests the following criteria<sup>49</sup>:

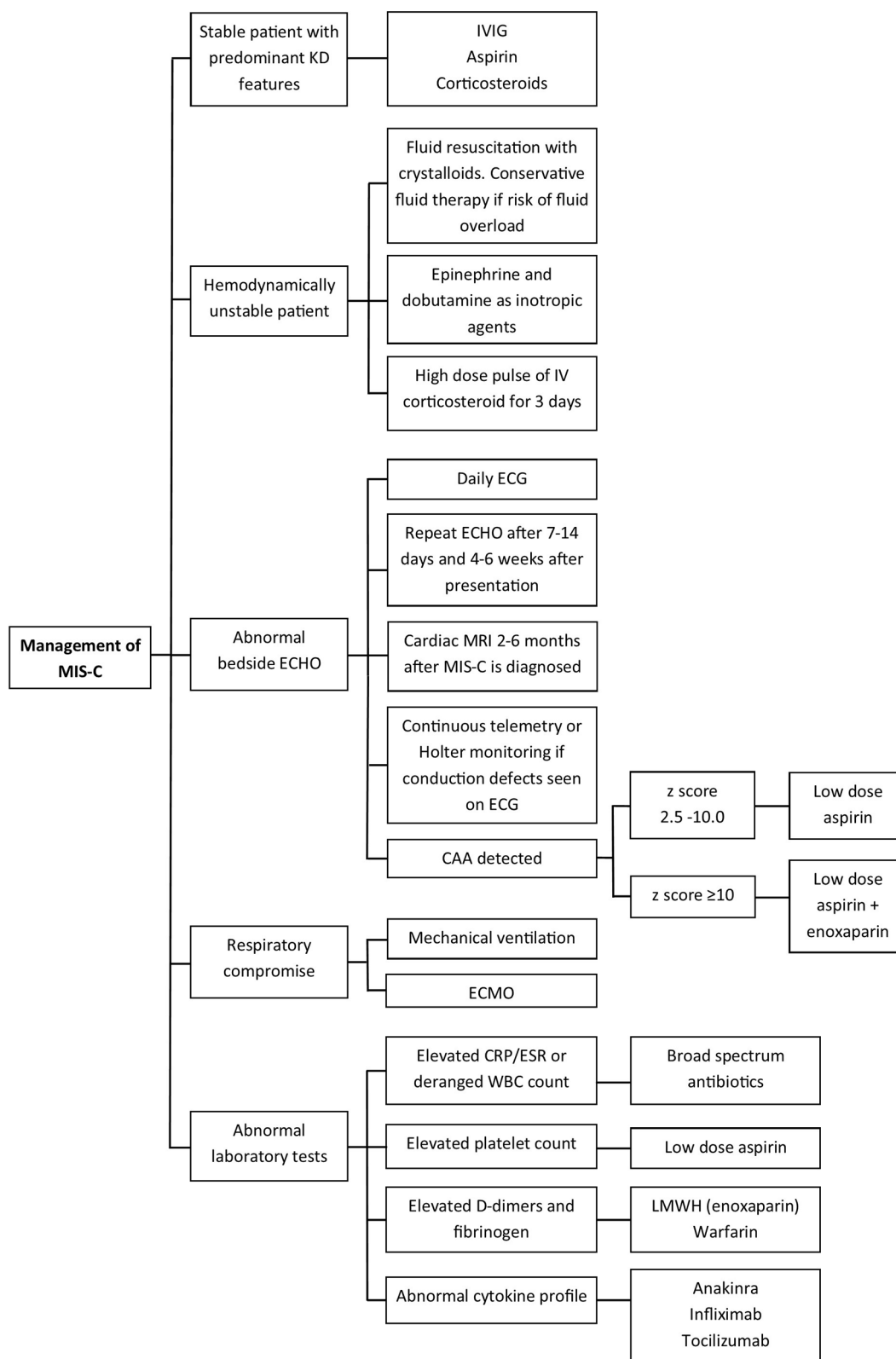
- Down-going trend of inflammatory markers (CRP, D-dimers, ferritin) for 3 to 4 days
- Decreasing TnT levels, currently  $< 1.0 \text{ mg/mL}$
- Forty-eight hours oxygen and vasopressor free
- Normal ECG
- Acceptable antifactor-Xa levels if the patient is being discharged on enoxaparin
- Adequate oral intake
- Controlled symptoms of heart failure if on medication, and improved ECHO findings including improved valve/wall function or normalisation of coronary arteries

Moreover, patients being discharged on steroids and/or biologics are given a 3-week tapering schedule.<sup>54</sup> All MIS-C patients are then advised to visit their primary care physician 2 to 3 days following discharge. While recommended follow up with their concerned specialist/s is after 2 weeks, patients are advised to return to the hospital if they suffer from fever ( $> 100.4^\circ\text{F}$ ), have recurring symptoms, or show signs of respiratory distress.<sup>48</sup>

### Cardiac Evaluation and Follow Up

While all patients are required to get an ECG done at presentation, unstable patients are recommended daily ECGs during hospital stay.<sup>11</sup> On the other hand, stable patients should get an ECG done every 48 hours, and then at every follow up visit. In cases where conduction defects are noted, continuous telemetry/Holter monitoring is needed.<sup>50</sup>

In patients where distal CAAs are suspected, cardiac CT may be helpful. Cardiac magnetic resonance imaging (MRI) is considered in patients 2 to 6 months after diagnosis, in those who suffered from significant transient or ongoing LV dysfunction. It is helpful in discerning the cause of myocardial injury (cytotoxic storm vs viral injury).<sup>11,50</sup>



**Figure 3.** Treatment pathway of MIS-C. Abbreviations: CAA, coronary artery aneurysm; CRP, C-reactive protein; ECG, electrocardiography; ECHO, echocardiography; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LMWH, low molecular weight heparin; MIS-C, multisystem inflammatory syndrome in children and adolescents; MRI, magnetic resonance imaging; WBC, white blood cell.<sup>45-53</sup>

An ECHO is advised at the time of admission, 7 to 14 days following presentation, and again after 4 to 6 weeks.<sup>50</sup> Alternatively, it can be done at the time of discharge, and again after 2 to 6 weeks

in order to identify any late changes, such as coronary artery dilatation.<sup>11,47</sup> While the standard time recommended for follow up is 2 weeks, this may be shortened for patients suffering from cardiac

complications during hospital stay.<sup>48</sup> Along with structural anomalies, this also includes patients with raised cardiac markers including TnT and NT-proBNP. These patients must also be considered for early follow up.<sup>52</sup> Additionally, a repeat ECHO after 1 year is advised for these patients.<sup>50</sup>

Prolonged follow up with enoxaparin is recommended in the following: patients whose z-score >10.0 requiring indefinite use; those with documented thrombosis for at least 3 months, depending on resolution; and patients with current moderate to severe LV dysfunction.<sup>50</sup> In patients who suffered from myocarditis, prolonged cardiac dietary restrictions and avoidance of vigorous exercise is recommended.<sup>54</sup>

### Rheumatology and Infectious Disease Follow Up

A follow up in the rheumatology department is recommended after 2 weeks with the following reports: CBC, CMP, CRP, ferritin, D-dimer, TnT and fibrinogen.<sup>48</sup>

Patients should see an infectious disease specialist either 1 week, or according to some, 4 weeks after discharge. Similar to other follow ups, basic laboratory tests should be on hand.<sup>48,49</sup>

Live vaccines are to be avoided for approximately 11 months following IVIG infusion. Additionally, the patient should be given their flu shot if discharged during flu season.<sup>48</sup>

A summarised version of the treatment can be seen below in Figure 3.

### Conclusion

MIS-C is an important sequela of COVID-19. Not only is there a need for its awareness to be spread amongst health care workers and parents alike, studies are also required in order to fully understand this diverse syndrome. With the increasing incidence of COVID-19 cases, it becomes even more important to be vigilant about the inevitable spike in MIS-C cases. Early diagnosis and treatment are key, along with strict follow up. While laboratory studies are required to determine its exact pathogenesis, long term clinical studies are needed to understand its sequelae and possible complications. Lastly, symptoms such as diarrhoea, fever and rash should not be neglected in the paediatric and adolescent population, especially when accompanied with a past history of COVID-19 infection.

### Author Contribution Statement

All authors of this study have contributed significantly, fulfilling the requirements for authorship. The details have been disclosed below: Ayesha Farooq: Conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, resources, writing – original draft, writing – review and editing. Fatima Alam: Conceptualisation, data curation, project administration, investigation, visualisation, supervision, writing – original draft, writing – review and editing. Asma Saeed: Conceptualisation, data curation, project administration, resources, visualisation, writing – original draft, writing – review and editing. Farooq Butt: Conceptualisation, data curation, project administration, resources, supervision, validation, writing

– original draft, writing – review and editing. Muhammad Azeem Khaliq: Data curation, investigation, methodology, resources, visualisation, writing – original draft, writing – review and editing. Ayesha Malik: Data curation, investigation methodology, resources, visualisation, writing – original draft. Manahil Chaudhry: Data curation, investigation, methodology, visualisation, validation, writing – original draft. Mohammad Abdullah: Conceptualisation, project administration, supervision, writing – review and editing.

### ORCID iDs

Ayesha Farooq  <https://orcid.org/0000-0003-0313-2837>

Mohammad Abdullah  <https://orcid.org/0000-0002-4650-7726>

### REFERENCES

1. Qazi SH, Saleem A, Pirzada AN, Hamid L-R, Dogar SA, Das JK. Challenges to delivering pediatric surgery services in the midst of COVID 19 crisis: experience from a tertiary care hospital of Pakistan. *Pediatr Surg Int*. 2020;36:1267-1273.
2. Covid: Merkel Warns of 'long, hard winter' as lockdowns return. *BBC News*. October 29, 2020. [www.bbc.com/news/world-europe-54728893](http://www.bbc.com/news/world-europe-54728893)
3. WHO coronavirus disease (COVID-19) dashboard. *World Health Organization*. November 2, 2020. [covid19.who.int/?gclid=EAIaIQobChMI3qi42vj06wIVQojVCh2v4Q9QEAAAYASAAEgI1XvD\\_BwE](https://covid19.who.int/?gclid=EAIaIQobChMI3qi42vj06wIVQojVCh2v4Q9QEAAAYASAAEgI1XvD_BwE)
4. Gopinath G. The great lockdown: worst economic downturn since the great depression. *IMF Blog*. April 14, 2020. [blogs.imf.org/2020/04/14/the-great-lockdown-worst-economic-downturn-since-the-great-depression/](https://blogs.imf.org/2020/04/14/the-great-lockdown-worst-economic-downturn-since-the-great-depression/)
5. Coronavirus disease 2019 (COVID-19) situation report – 51. *World Health Organization*. March 11, 2020. [www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57\\_10](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10)
6. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med*. 2020;26:1205-1211.
7. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145:e20200702.
8. Ciuca IM. COVID-19 in children: an ample review. *Risk Manag Healthc Policy*. 2020;13:661-669.
9. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395:1771-1778.
10. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395:1607-1608.
11. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020;20:e276-e288.
12. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19). *Centers for Disease Control and Prevention*. May 14, 2020. [emergency.cdc.gov/han/2020/han00432.asp](https://emergency.cdc.gov/han/2020/han00432.asp)
13. Freedman S, Godfred-Cato S, Gorman R, et al. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. *World Health Organization*. May 15, 2020. [www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19](https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)
14. Kim H, Shim JY, Ko J-H, et al. Unusual presentation of Kawasaki disease with multisystem inflammation and antibodies against severe acute respiratory syndrome coronavirus 2: a case report. *Res Sq*. Published online July 15, 2020. doi:10.21203/rs.3.rs-41276/v1
15. CDC. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. *Centers for Disease Control and Prevention*. July 15, 2020. [web.archive.org/web/20200717095454/www.cdc.gov/mis-c/cases/](https://web.archive.org/web/20200717095454/www.cdc.gov/mis-c/cases/)
16. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. *J Pediatr*. 2020;226:45-54.
17. Shang J, Zhang Y, Yang Y, et al. Cryo-EM structure of infectious bronchitis coronavirus spike protein reveals structural and functional evolution of coronavirus spike proteins. *PLoS Pathog*. 2018;14:e1007009.
18. Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV: a comparative overview. *Infez Med*. 2020;28:174-184.

19. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004;203:631-637.
20. Qinfen Z, Jinning C, Xiaojun H, et al. The life cycle of SARS coronavirus in vero E6 cells. *J Med Virol.* 2004;73:332-337.
21. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol.* 2017;39:529-539.
22. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* 2020;53:25-32.
23. Conti B, Tabarean I, Andrei C, Bartfai T. Cytokines and fever. *Front Biosci.* 2004;9:1433-1439.
24. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol.* 2020;20:529-536.
25. Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19-related multisystem inflammatory syndrome in children. *J Clin Invest.* 2020;130:5619-5621.
26. Capone CA, Subramony A, Sweberg T, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. *J Pediatr.* 2020;224:141-145.
27. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell.* 2020;183:982-995.
28. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol.* 2020;7:575-582.
29. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol.* 2020;5:751-753.
30. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation.* 2020;142:429-436.
31. Mao R, Qiu Y, He J-S, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2020;5:667-678.
32. Liang W, Feng Z, Rao S, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. *Gut.* 2020;69:1141-1143.
33. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. *Clin Gastroenterol Hepatol.* 2020;18:1663-1672.
34. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol.* 2020;95:834-847.
35. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol.* 2020;7:438-440.
36. Guarneri C, Venanzi Rullo E, Pavone P, et al. Silent COVID-19: what your skin can reveal. *Lancet Infect Dis.* 2020;21:24-25.
37. Magro C, Justin Mulvey J, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res.* 2020;220:1-13.
38. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med.* 2020;8:738-742.
39. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* 2020;277:2251-2261.
40. Needham EJ, Chou SH-Y, Coles AJ, Menon DK. Neurological implications of COVID-19 infections. *Neurocrit Care.* 2020;32:667-671.
41. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77:683-690.
42. The Children's Hospital of Philadelphia. *Multisystem Inflammatory Syndrome (MIS-C) Clinical Pathway – Emergency, ICU and Inpatient.* The Children's Hospital of Philadelphia; 2020. [www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway](http://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway)
43. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children.* 2020;7:69.
44. Jajodia A, Ebner L, Heidinger B, Chaturvedi A, Prosch H. Imaging in corona virus disease 2019 (COVID-19)—a scoping review. *Eur J Radiol Open.* 2020;7:100237.
45. Boston Children's Hospital. Multisystem Inflammatory Syndrome in Children (MIS-C): Boston Children's Hospital. *Boston Childrens Hospital.* 2020. [www.childrenshospital.org/conditions-and-treatments/conditions/m/mis-c](http://www.childrenshospital.org/conditions-and-treatments/conditions/m/mis-c)
46. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr.* 2020;10:537-540.
47. Grimaud M, Starck J, Levy M, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Intensive Care.* 2020;10:69.
48. The Children's Hospital of Philadelphia. *Multisystem Inflammatory Syndrome (MIS-C) – Discharge Instructions and Follow-up Plan – Clinical Pathway: Emergency, ICU and Inpatient.* The Children's Hospital of Philadelphia; 2020. [www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-discharge-instructions-and-follow-up-plan](http://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-discharge-instructions-and-follow-up-plan)
49. Hennon TR, Penque MD, Abdul-Aziz R, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines; a western New York approach. *Prog Pediatr Cardiol.* 2020;57:101232.
50. Henderson LA, Canna SW, Friedman AG, et al. American college of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. *Arthritis Rheumatol.* 2020;72:1791-1805.
51. Alhazzani W, Hylander Møller M, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med.* 2020;46:854-887.
52. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA.* 2020;324:259.
53. Leon MPD, Redzepi A, McGrath E, et al. COVID-19-associated pediatric multisystem inflammatory syndrome. *J Pediatric Infect Dis Soc.* 2020;9:407-408.
54. American Academy of Pediatrics. Multisystem-inflammatory syndrome in children (MIS-C) interim guidance. *American Academy of Pediatrics.* January 9, 2020. [services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/](http://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/)
55. Sosa TK, Shah SS. What is the role of aspirin in the treatment of Kawasaki disease? Latest Medical News, Clinical Trials, Guidelines - Today on Medscape. *Medscape.* July 29, 2018. [www.medscape.com/answers/965367-117441/what-is-the-role-of-aspirin-in-the-treatment-of-kawasaki-disease](http://www.medscape.com/answers/965367-117441/what-is-the-role-of-aspirin-in-the-treatment-of-kawasaki-disease)
56. Sakulchit T, Benseler SM, Goldman RD, et al. Acetylsalicylic acid for children with Kawasaki disease. *Can Fam Physician.* 2017;63:607-609.
57. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol.* 2020;2:393-400.
58. Taylor SA, Vittorio JM, Martinez M, et al. Anakinra-induced acute liver failure in an adolescent patient with still's disease. *Pharmacotherapy.* 2016;36:e1-e4.
59. National Cancer Institute, Naples. Tocilizumab in COVID-19 pneumonia (TOCIVID-19). *Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) – Full Text View – ClinicalTrials.gov.* March 20, 2020. [clinicaltrials.gov/ct2/show/NCT04317092](https://clinicaltrials.gov/ct2/show/NCT04317092)
60. Health Service Executive. Interim Guidance for the Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 with Suspected Hyperinflammation. *HSE.* August 21, 2020. <https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/hse-interim-guidance-for-the-use-of-tocilizumab-in-the-management-of-hospitalised-patients-with-severe-covid-19-disease-v6.pdf>
61. Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet.* 2020;395:1407-1409.
62. Dolinger MT, Person H, Smith R, et al. Pediatric Crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. *J Pediatr Gastroenterol Nutr.* 2020;71:153-155.