JPPT | State of the Art Review

The Trilogy of SARS-CoV-2 in Pediatrics (Part 2): Multisystem Inflammatory Syndrome in Children

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Multisystem Inflammatory Syndrome in Children (MIS-C) was first recognized as a novel illness in 2020 with manifestations similar to other hyperinflammatory syndromes, such as Kawasaki disease or macrophage activation syndrome. Severity varies from a self-limited febrile illness to shock requiring inotropes and mechanical ventilation. Gastrointestinal symptoms and persistent fevers are the most common clinical symptoms, with the addition of cardiac manifestations inclusive of ventricular dysfunction and coronary artery aneurysms. With no controlled trials or comparative effectiveness studies evaluating treatment of MIS-C to date, current treatment with immunomodulatory agents has mainly been derived from previous experience treating Kawasaki disease. This article provides a comprehensive review summarizing published data for the evaluation and management of MIS-C, with a focus on pharmacotherapy treatment considerations.

ABBREVIATIONS ACE2, angiotensin-converting enzymes 2; ACR, American College of Rheumatology; ADR, adverse drug reaction; ASA, aspirin; BNP, B-type Natriuretic Peptide; CAA, coronary artery aneurysms; CDC, US Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; CRP, C-reactive protein; CT, computed tomography; ECHO, echocardiogram; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; FDA, US Food and Drug Administration; HLH, hemophagocytic lymphohistiocytosis; IBW, ideal body weight; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; MMR, measles-mumps-rubella; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; OR, odds ratio; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PRISM, Pediatric Research Immune Network on SARS-CoV-2 and MIS-C; PT, prothrombin time; PTT, partial thromboplastin time; RR, risk ratio; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; TBW, total body weight; TLR, Toll-like receptor; TMPRSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor α; WHO, World Health Organization

KEYWORDS children; coronavirus-19; MIS-C; multisystem inflammatory syndrome in children; pediatric; PIM-TS; SARS-CoV-2

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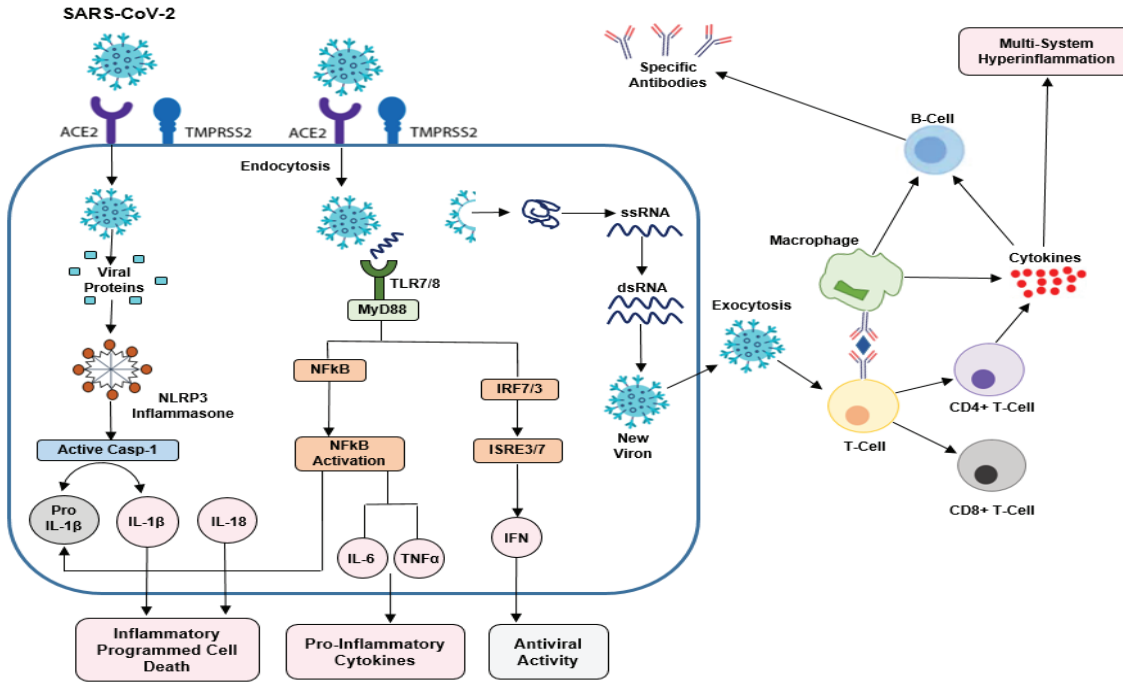
Editor's Note *In this issue of the Journal of Pediatric Pharmacology and Therapeutics, we continue a series of 3 interconnected manuscripts focused on COVID-19 disease, caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). This first Paper, which was published in the third issue of this year, succinctly reviewed what is known about this challenging disease with a focus on special populations. Part 2 – The Trilogy of SARS-CoV-2 in Pediatrics: Multisystem Inflammatory Syndrome in Children will appear in this the fourth issue and the final paper – Part 3: The Trilogy of SARS-CoV-2 in Pediatrics: Anticoagulation and Antiplatelet Considerations will appear in an upcoming issue later this year. Our primary goal with these publications is to continue to disseminate timely, comprehensive, peer-reviewed information on this disease and how this virus effects children of all ages. The information contained in these three publications will compliment your ongoing efforts in staying contemporary with the scientifically sound, evidence-based research and clinical data for incorporation into your daily practice.*

– Michael D. Reed, PharmD, Associate Editor

Introduction

A novel inflammatory illness in children temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in April 2020. Such cases appeared to develop during the weeks following a peak in coronavirus disease 2019 (COVID-19) cases across the globe.[1] This new inflammatory illness presenting with multiorgan involvement soon

Figure 1. Predicted MIS-C pathophysiology.



ACE2, angiotensin-converting enzyme 2; dsRNA, double-stranded ribonucleic acid; IFN, interferon; IL, interleukin; ISRE, interferon-stimulated response element; IRF, interferon regulatory factor; NFkB, NF-κ B; MYD88, myeloid differentiation primary response 88; NLRP3, nucleotide-binding oligomerization domain and leucine-rich repeat containing protein 3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, Toll-like receptor; TMPRSS2, transmembrane protease serine 2; TNFα, tumor necrosis factor α; ssRNA, single-stranded ribonucleic acid

became known as Pediatric Multisystem Inflammatory Syndrome–Temporally Associated with SARS-CoV-2, or Multisystem Inflammatory Syndrome in Children (MIS-C).[1-4] As of April 5, 2021, CDC has reported a total of 3,185 MIS-C cases meeting case definition, with 36 deaths.[5] Clinical manifestations of MIS-C vary; however, many present with symptoms similar to Kawasaki disease (KD), KD shock syndrome, toxic shock syndrome, and macrophage activation syndrome (MAS).[6] The exact incidence of MIS-C is unknown but has been estimated to be 11.4 cases per 100,000 population younger than 20 years among MIS-C cases reported to the New York City Department of Health and Mental Hygiene from March to June 2020.[7] This was an increase from the first estimate of 2 in 100,000 individuals for New York City residents younger than 21 years from March to May 2020 and an estimated incidence of laboratory-confirmed SARS-CoV-2 infection of 322 per 100,000.[1] Observed spikes in the incidence of MIS-C appear to correlate with demographic spikes in COVID-19 representing the delayed onset. This has been distinctively evident surrounding the recent post-holiday COVID-19 spike. It is important to note that our review is current as of April 8, 2021, and is subject to change as the SARS-CoV-2 pandemic continues to evolve.

Acute COVID-19 Infection in Pediatrics

SARS-CoV-2 is the virus responsible for the clinical disease known as COVID-19. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic.[1,8] Acute respiratory failure and multiorgan failure are the most common complications observed in adults with acute COVID-19 infections.[9] Children appear to be disproportionately affected and are often spared from the life-threatening complications of COVID-19.[9] Please refer to part 1 of our trilogy series for in-depth evaluation and management of acute COVID-19 infection in pediatric patients.[10]

The Age Divide. The remarkable difference in disease severity in relation to patient age is referred to as the COVID-19 age divide.[11] To understand the proposed pathophysiology of MIS-C, it is imperative to recognize the mechanisms by which SARS-CoV-2 gains cellular entry, replicates, and engages the hyperimmune response. Please refer to part 1 of our trilogy series for an in-depth review of the pathophysiology, evaluation, and management of acute COVID-19 infection in pediatric patients.[10] Specific physiologic differences may help explain this division.[9]

We wish to highlight a few possible reasons for this divide. Compared with adults, children have signifi-

cantly lower angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) expression within epithelial lung cells.[11] This physiologic variation is thought to provide children innate protection within the lower respiratory tract against SARS-CoV-2 invasion. ACE2 is essential for the conversion of angiotensin-2 to angiotensin. Failed conversion and accumulation of angiotensin-2 is associated with severe inflammation, vasoconstriction, and increased vascular dysfunction.[12] The combination of ACE2 overexpression and angiotension-2 accumulation substantiates one of many possible sources of heightened inflammation commonly noted in adults.

The immune response to COVID-19 differs remarkably between children and adults. Once infected, adults have a greater likelihood of progressing to a state of hyperinflammation. Adults naturally produce higher levels of inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and IL-1β, and may therefore be more vulnerable to this COVID-19 hyperinflammatory state.[13] Conversely, children produce less inflammatory cytokine and efficiently produce modulatory cytokines, such as IL-10 and IL-13. The underlying origin of the vast variations in cytokine production observed between children and adults remains largely elusive.

The measles-mumps-rubella (MMR) vaccine has been theorized to provide protection against COVID-19. One study evaluated the correlation of MMR immunoglobulin G (IgG) titers with disease severity in recovered COVID-19 patients.[14] Results revealed an association between high mumps titers (134–300 AU/mL) and COVID-19 patients who were found to be asymptomatic and/or functionally immune. Low mumps titer values (below 75 AU/mL) were associated with moderate and severe cases of COVID-19. Similar associations were not identified for measles or rubella titers. A statistically significant inverse correlation was determined, indicating a potential relationship between mumps titers and COVID-19 severity. Although this finding supports the theorized association between MMR vaccine and COVID-19 severity, further investigation is warranted.

The combination of ACE-2 and TMPRSS2 expression, T-cell response, mumps IgG titers, and superior inflammatory modulation are all likely contributors to the decreased prevalence, severity, and mortality associated with COVID-19 disease in children.[13] Although pediatric patients are rarely affected by the initial COVID-19 infection, they are not fully spared. Documented cases of MIS-C, a rare postinfectious antibody-mediated syndrome, continue to increase as the pandemic persists.[9]

Pathophysiology of MIS-C

COVID-19 hyperinflammation is multifaceted, comprising Toll-like receptors (TLRs), IL-1, interferons (IFNs), IL-18, IL-6, IL-8, IFN-α, and IL-10.[15,16] Research to identify the specific factors responsible for the vast variations in the SARS-CoV-2 immune response is ongoing. IL-1 is supported by the strongest evidence and will be of primary focus; IFN will also be discussed in brief, as will other proinflammatory and modulating cytokines (Figure 1).

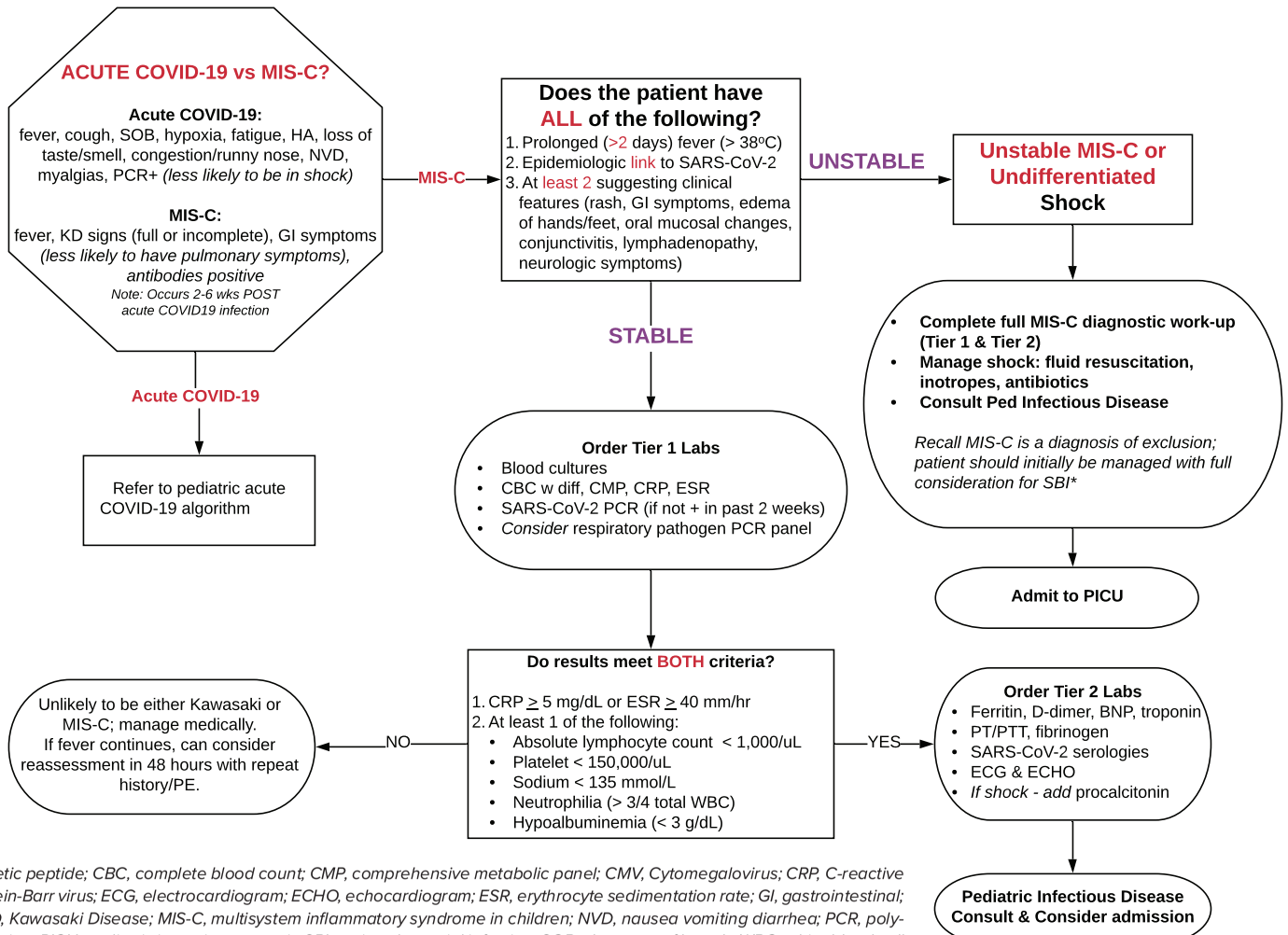
Interleukin-1. Interleukin-1 is a cytokine with 2 distinct coding genes, IL-1α and IL-1β.[17] Both of these bind via the IL-1 receptor 1 (IL-1R1). IL-1α is a biologically active potent fever-producing molecule. IL-1β is a precursor which is activated via proteolytic cleavage. Capsase-1, a cysteine protease, is responsible for cleaving and activating IL-1β. A complex of intracellular proteins, known as an inflammasome, must be assembled in order to activate capsase-1. In addition, IL-1α and IL-1β are capable of self-induction, promoting preservation of the ongoing autoinflammation. Interestingly, SARS-CoV-2 is independently capable of activating the inflammasome. The mere presence of SARS-CoV-2 viral proteins is capable of inflammasome activation and subsequent enzymatic activation of IL-1β.[16,18] Activation of IL-1β, specifically if uncontrolled or uninhibited, possesses the capability of inducing catastrophic system inflammation, multiorgan failure, and possibly death.[17]

Interleukin-1–mediated inflammation manifests broadly throughout the body, affecting the ears, lungs, liver, kidneys, brain, eyes, pancreas, lymph nodes, skin, joints, and bone marrow.[17] In addition, IL-1 stimulates downstream expression of multiple cytokines and activation of T cells, thereby priming the adaptive immune response.[18] Excessive or uninhibited IL-1β production is a primary contributor for immune response dysregulation related to COVID-19–associated and MIS-C–associated morbidity and mortality.[17,19]

Genetic predisposition and/or SARS-CoV-2 superantigen-like characteristics are highly suspected to contribute to the overall pathogenesis of MIS-C.[18] Particular genetic traits are thought to potentiate nucleotide-binding oligomerization domain and leucine-rich repeat containing proteins 3 (NLRP3) activation and immune dysregulation; however, such specifics will not be discussed in this review.[18] Superantigens (i.e., *Streptococcus* and *Staphylococcus* species) are known to be potent inducers of IL-1β, T cells, and B cells, and complement pathways, resulting in hyperinflammation. SARS-CoV-2 possesses intrinsic superantigen-like properties and shares motifs similar to that of staphylococcal endotoxins.

Interferon. Once SARS-CoV-2 binds to the host cell, the IFN response is engaged. Following endocytosis, replication, and assembly, the viral load steadily rises.[15] Interferon is known to aid in viral clearance, resulting in milder disease. In a select subset of patients, the viral load is thought to rapidly rise and/or the innate immune response is abnormally slow. This delay postpones engagement of the host IFN response. A cytokine cascade is induced, destabilizing balance and leading to

Figure 2. Emergency Department Initial Evaluation of MIS-C.[41]



BNP, brain natriuretic peptide; CBC, complete blood count; CMP, comprehensive metabolic panel; CMV, Cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; ECG, electrocardiogram; ECHO, echocardiogram; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HA, headache; KD, Kawasaki Disease; MIS-C, multisystem inflammatory syndrome in children; NVD, nausea vomiting diarrhea; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; SBI, serious bacterial infection; SOB, shortness of breath; WBC, white blood cell

* Differential diagnosis includes bacterial sepsis, toxic shock syndrome, Kawasaki Disease (KD), appendicitis, hemophagocytic lymphohistiocytosis (HLH) ormacrophage activation syndrome (MAS), Rickettsia, viral syndrome (CMV, EBV, Adenovirus, Enteroviruses, varicella, etc.), bacterial enteritis, lupus, vasculitis, and other conditions.

Kawasaki Disease (complete must have 4 of 5; incomplete must have 2 of 5 and supporting labs [Circulation 2017]):
Fever (4-5 days), conjunctivitis, rash, edema (hands/feet), AND lymphadenopathy (1.5 cm)

significant systemic hyperinflammation. Subsequently, IFN signals killer CD8 cytotoxic T cells into the already inflamed tissue, further intensifying this inflammatory cascade. This process is specifically prominent in the heart and thought to be directly involved in MIS-C–associated cardiovascular manifestations.

Cardiac Manifestations. Studies in recovered adults previously infected with COVID-19 demonstrated ongoing myocardial inflammation and cardiac involvement.[20] ACE2 receptors are present on various epithelial and endothelial cells throughout the body, with abundance in the heart, lungs, intestines, kidneys, and arteries. As expected, these organs are the most common organ systems affected by MIS-C. MIS-C and MAS share similar clinical features, including systemic uninhibited inflammation, associated multiorgan failure, and disseminated intravascular coagulation. MIS-C–associated cardiac manifestations occur at a surprisingly high rate. Remarkably, many patients present with normal initial echocardiograms (ECHOs). However, on follow-up, ECHOs reveal depressed ejection fractions, dilation coronary arteries, and/or cardiac artery aneurysms (CAAs).

SARS-CoV-2 binds to the ACE2 receptors of cardiac endothelial cells, inducing cardiovascular damage via direct cardiomyocyte toxicity, endotheliitis, hypercoagulability, and microvascular injury.[20,21] The incidence of CAAs in patients with MIS-C is lower in comparison with patients with KD; however, MIS-C carriers a higher incidence of depressed ejection fractions, myocarditis, and/or pericarditis.[20,21]

Specific risk factors in adults and children, such as atherosclerosis or Ehlers-Danlos syndrome, may place an individual at a higher risk of CAAs secondary to SARS-CoV-2 myocarditis.[18] Children have a higher likelihood of aneurysm development secondary to ongoing growth. Individuals with disease states known to impact the integrity of the internal elastic lamina of the arteries may also be at a higher risk of CAAs.[18]

Clinical Outcomes. The vast majority of patients with MIS-C present with mild to moderate involvement, require no to minimal clinical intervention, and recover fully in the absence of sequelae.[20] Patients presenting with severe MIS-C should receive prompt treatment to minimize the risk of acute decompensation. The short-term clinical outcomes in patients with MIS-C have been described in various published case reports, case series, case-control, and cross-sectional studies. One systematic review that included 39 observational studies encompassing 662 children with a diagnosis of MIS-C reported ICU admission in 71% of patients and mortality occurring in 1.7%. Mechanical ventilation was required in 22.2%, with 4.4% of patients requiring extracorporeal membrane oxygenation (ECMO).[20] Of the ECHOs conducted on 88% of patients, more than half (54%) had abnormalities reported. The most commonly encountered cardiac abnormality was depressed left ventricular ejection fraction (45.1%). Additional reported cardiovascular outcomes included pericardial effusion/pericarditis (22%), aneurysms (8.1%), and coronary dilation (7.6%). Standardized follow-up recommendations for patients with MIS-C are still evolving.[18]

Cardiology reassessments and follow-up should be geared toward the type and severity of MIS-C.[18] If adapting from the KD treatment guidelines, an ECHO should be obtained at baseline and repeated as clinically necessary up to 6 to 8 weeks after. If the baseline ECHO is abnormal, repeat ECHOs should be more frequent, especially during the first week. Once the clinical trajectory is better established, repeat ECHOs may be spaced out. Current recommendations advise considering a cardiac MRI 3 months after MIS-C to help stratify long-term risks and follow-up requirements.

The long-term outcomes of children with MIS-C have yet to be defined.[20] The National Institutes of Health recently launched a study (NCT04588363) known as the Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM). PRISM is a nationwide, multicenter, observational study aimed at providing information on the clinical spectrum of COVID-19, long-term outcomes, and the underlying immunologic pathophysiology of MIS-C specific to children and young adults. PRISM has 2 primary objectives, the first to determine the rate of deaths, rehospitalization, and SARS-CoV-2–induced health complications at 6 months and 12 months after COVID-19, MIS-C, or both.[22] The second objective is to define the immunologic mechanisms and associated characteristics linked with the various forms of MIS-C and pediatric COVID-19. The results from the PRISM study are anticipated to help fill in the current knowledge gaps.

Evaluation

In the absence of a "gold standard" test, the American College of Rheumatology (ACR) recommends using a stepwise approach for diagnosing MIS-C.[19] The relative rarity of MIS-C should be considered in this diagnostic approach. A tiered diagnostic approach is recommended to assist providers in patients without life-threatening manifestations (Figures 2 and 3). The initial screening evaluation (tier 1) should evaluate clinical symptoms and include the following laboratory tests: complete blood cell count with manual differential, complete metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and testing for SARS-CoV-2 via PCR or serology. If tier 1 laboratory results are concerning, the provider is further prompted to proceed to tier 2, encompassing a more comprehensive diagnostic approach. Institution-specific guidelines including a tailored diagnostic tiered approach are highly recommended.

Clinical Presentation and Laboratory Findings. Although fever for at least 4 days is the *sine qua non* of MIS-C, it is rather non-specific. MIS-C patients can

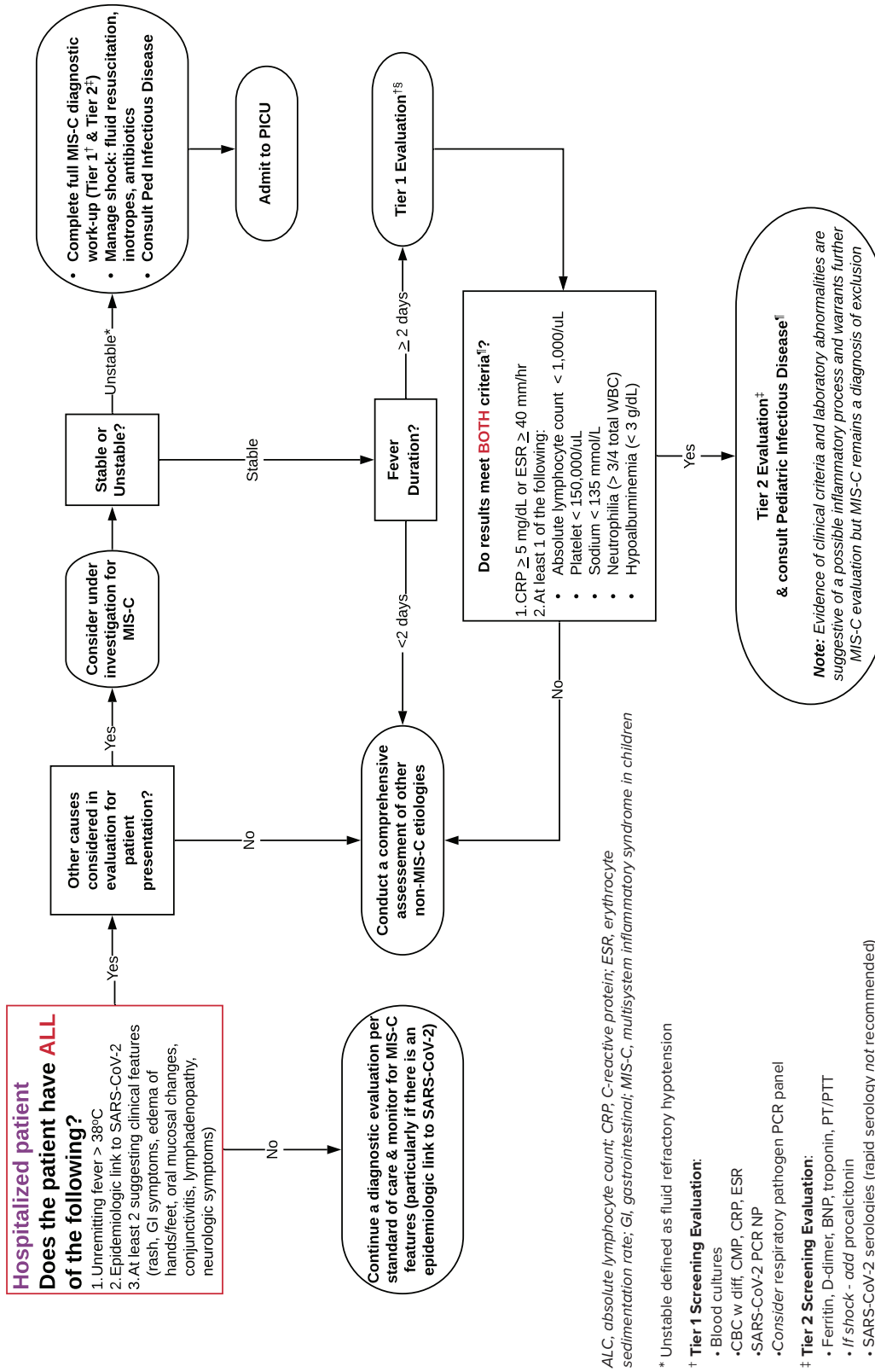


Figure 3. Inpatient Initial Evaluation of MIS-C.[41]

ALC, absolute lymphocyte count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; MIS-C, multisystem inflammatory syndrome in children

* Unstable defined as fluid refractory hypotension

† **Tier 1 Screening Evaluation**:
- Blood cultures
- CBC w diff, CMP, CRP, ESR
- SARS-CoV-2 PCR NP
- *Consider* respiratory pathogen PCR panel

‡ **Tier 2 Screening Evaluation**:
- Ferritin, D-dimer, BNP, troponin, PT/PTT
- *If shock - add* procalcitonin
- SARS-CoV-2 serologies (rapid serology *not* recommended)
- EKG & ECHO

§ **If SARS-CoV-2 RT-PCR** nasopharyngeal swab was obtained within the last 2 weeks, defer PCR testing. If previously negative, then obtain another.

¶ *Evidence of clinical criteria and laboratory abnormalities are suggestive of a possible inflammatory process and warrants further MIS-C evaluation*

Table 1. Overlapping Features of Kawasaki Disease and Multisystem Inflammatory Syndrome in Children[20]

Characteristics	Kawasaki Disease	Multisystem Inflammatory Syndrome in Children
Age	<5 years	Mean: 9.3 ± 0.4 years
Ethnicity (higher risk)	East Asian descent	African descent Hispanic descent
Sex (higher risk)	Males	Males
Clinical signs and symptoms	Conjunctivitis (bilateral, non-purulent) Rash (non-vesicular, no bullae) Adenopathy (cervical, typically unilateral) Oropharyngeal changes (red/cracked lips, strawberry tongue, erythema of oral/pharyngeal mucosa) Extremity changes (edema/erythema hands or feet) Fever (5 or more days)	Conjunctivitis (bilateral, non-purulent) Rash Adenopathy (cervical) Oropharyngeal changes (red/cracked lips, strawberry tongue, erythema of oral/pharyngeal mucosa) Extremity changes (edema/erythema hands or feet) Fever (3 or more days) Gastrointestinal symptoms (vomiting, diarrhea, abdominal pain) Neurologic symptoms (headache, irritability, altered mental status, encephalopathy, seizures)
Cardiovascular involvement	25% coronary artery aneurysms if untreated 5% cardiovascular collapse 10% shock	20% cardiac dysfunction (arrhythmias and ventricular dysfunction) 60.2% shock
Laboratory	↓ Platelet counts ↓ Lymphocyte counts ↑ C-reactive protein	↓↓ Platelet counts ↓↓ Lymphocyte counts ↑↑ C-reactive protein

present with a range of clinical findings secondary to the widespread systemic inflammation. These findings may include abdominal pain, diarrhea, erythema and cracking of the lips, conjunctivitis, and rash.[23,24] Additionally, as noted above, MIS-C often affects the cardiovascular system, resulting in hypotension and shock requiring intensive care and use of vasopressor or ionotropic support.[9,24,25]

Respiratory dysfunction has been reported in patients with MIS-C. Of the cases requiring mechanical ventilation, cardiovascular manifestations were common, and mechanical ventilation was primarily used for cardiovascular support.[26] Furthermore, a minority of patients with MIS-C have required ECMO.[25] Acute kidney injury and deep vein thrombosis have been reported but are less common in MIS-C. Although the MIS-C case definition requires involvement of at least 2 organ systems, involvement of at least 4 organ systems may be a better predictor and aid in narrowing the differential diagnosis.[9,27] Lymphopenia, thrombocytopenia, and elevations in CRP, ESR, procalcitonin, D-dimer, fibrinogen, and ferritin are commonly observed in patients presenting with MIS-C.[28] Disease severity has been linked with the severity of inflammatory marker elevation. Additionally, many present with elevated troponin and brain natriuretic peptide (BNP) related to cardiac involvement.[18] To date, no relationship between the degree of BNP elevation and MIS-C disease severity has been established.

Comparison to KD. Kawasaki disease is an acute vasculitis of childhood with an unknown cause and predilection for coronary artery complications.[29] Kawasaki disease is the leading cause of acquired heart disease in children in developed countries, and if left untreated it can lead to CAA. Similar coronary artery dilation has been observed in patients with MIS-C; however, the long-term implications of this are not yet understood.

Although KD and MIS-C may present with similar clinical features, the two differ in several ways (Table 1). In comparing the 2 clinical entities, MIS-C presents later in childhood, with an average age around 9 years. Additionally, some studies have highlighted a slight male predominance.[23,26,28] Although autoantibodies have been detected in patients with KD and MIS-C, researchers have determined that T-cell subsets may be unique to KD.[30] Furthermore, there are specific key differences in lab abnormalities between KD and MIS-C, with lymphopenia and markedly elevated inflammatory markers often seen primarily in MIS-C.[31] Northern Virginia data from A. Nuibe, MD (email communication, February 2021), verifies MIS-C patients tend to have lab abnormalities differing from those seen in contemporaneous KD cases. In comparing 7 KD cases to 14 MIS-C cases during the same period of time, we observed an initial absolute lymphocyte count of 2860/μL in KD cases versus 1330/μL in MIS-C cases ($p < 0.01$), an initial platelet count of 367,000/μL in KD cases versus 193,000/μL in MIS-C cases ($p = 0.03$), and an initial CRP

Table 2. Comparison of Multisystem Inflammatory Syndrome in Children Criteria[19,39,40]

Criteria	CDC (All of the Following Must Be Met)	WHO (All of the Following Must Be Met)
Age	<21 yr	≤19 yr
Fever	Documented (≥ 38°C) for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours	≥3 days
Clinical symptoms	*Both* of the following: 1. Evidence of clinically severe illness requiring hospitalization 2. Multisystem (≥2) organ involvement (cardiac, respiratory, hematologic, renal, gastrointestinal, dermatologic, or neurological)	*Two* of the following: 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP) 4. Coagulopathy (by PT, PTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
Laboratory markers of inflammation	≥1 of the following (but not limited to): ↑ CRP ↑ Erythrocyte sedimentation rate ↑ Fibrinogen ↑ Procalcitonin ↑ D-dimer ↑ Ferritin ↑ Lactic acid dehydrogenase ↑ Interleukin 6 Neutrophilia Lymphopenia Hypoalbuminemia	Elevated markers of inflammation, including any of the following: ↑ CRP ↑ ESR ↑ Procalcitonin
Link to SARS-CoV-2	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 week prior to the onset of symptoms	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.
Exclusion	No alternative plausible diagnoses	No other obvious microbial cause

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECHO, echocardiogram; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal pr b-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

of 11.2 mg/dL in KD cases versus 23.2 mg/dL in MIS-C cases ($p < 0.01$).

Virologic, Antigen, and Serologic Tests. Kawasaki disease and MIS-C may present similarly, and both can result in coronary artery changes; thus, distinguishing one entity from another is challenging. However, because of MIS-C's initial description, evidence has supported a temporal association with COVID-19 activity. Hence, the current US MIS-C diagnostic criterion involves the diagnosis of a recent SARS-CoV-2 infection via a positive SARS-CoV-2 reverse transcription PCR (RT-PCR), serology, or antigen; alternately, exposure to a COVID-19 case within 4 weeks of MIS-C symptoms can also define MIS-C.[5]

Because SARS-CoV-2 can be asymptomatic in children and because MIS-C appears to follow a SARS-CoV-2 infection, simultaneous SARS-CoV-2 nucleic acid amplification testing and SARS-CoV-2 IgG are currently recommended to accurately diagnose MIS-C.[32] At this time, it is unknown whether laboratory confirmation of a recent SARS-CoV-2 illness via molecular testing, serology, or antigen testing is best for diagnosing MIS-C.

Radiologic Findings. MIS-C remains a clinical diagnosis, and there are no defining radiologic features for this syndrome. Chest radiographs may be normal, especially in the absence of respiratory or cardiac manifestations as part of the presenting illness. Alternately, chest radiographs of patients with MIS-C can show non-specific peribronchial cuffing and perihilar interstitial thickening progressing to perihilar airspace opacification, pulmonary edema, pleural effusion, and cardiomegaly, with associated cardiac dysfunction,

Table 3. Multisystem Inflammatory Syndrome in Children Case Severity[41,42]

Severity	Description
Mild	Does not require admission to the PICU Minimal organ injury Minimal or no respiratory support*
Moderate	May or may not require admission to the PICU Mild or isolated organ injury Requires respiratory support*
Severe	Admission to the PICU Moderate-severe organ injury† and/or ventricular dysfunction Requires non-invasive or invasive ventilator support Requiring inotropic support

* Respiratory support is defined as requiring significant supplemental oxygen (≥2 l/min of oxygen for patients age <12 yr, or ≥6 l/min of supplemental oxygen for patients age ≥12 yr) from baseline.

† Moderate-severe organ injury includes fluid-refractory hypotension for age, renal or hepatic insufficiency, or respiratory distress/failure.

shock and/or fluid resuscitation.[33,34] Children who required respiratory support may have diffuse chest radiograph findings, including ground-glass opacities and pleural infusions similar to acute respiratory distress syndrome.[33,34] There has been variable reports of hilar and/or mediastinal lymphadenopathy reported on CT chest imaging.[33,35] Few patients with MIS-C were found to have small segmental pulmonary emboli.[33,35] Cardiac MRI was completed in 1 case series of MIS-C children which showed diffuse myocardial signal hyperintensity of the left ventricle, suggesting interstitial edema.[36] Children with elevated BNP or other evidence of cardiogenic shock tended to have abnormal chest imaging.[33,35]

Almost all children undergo cardiac echocardiography to assess for coronary artery dilation and evidence of myocarditis. In 1 study comparing healthy controls to KD and MIS-C cases, ECHOs showed that coronary artery disease could be absent in early MIS-C compared with KD, but that myocardial injury was more common in MIS-C, even if the ejection fraction was preserved.[37] In spite of these abnormalities, short-interval follow-ups of MIS-C patients revealed recovery of systolic function but persistence of diastolic dysfunction, without development of coronary aneurysms. In MIS-C cases presenting with gastrointestinal symptoms, imaging findings also range from normal to abnormal. Ultrasounds have shown anechoic free fluid/ascites, inflammatory fat stranding, mesenteric lymphadenopathy, hepatomegaly, gallbladder wall thickening, bowel wall thickening, increased renal echogenicity, splenomegaly, and/or urinary bladder wall thickening with similar findings on abdominal CT.[33-35,38]

Case Definitions. Official definitions were released by the CDC and the WHO almost simultaneously in mid-May 2020.[39,40] The definitions remain unchanged and are similar but not identical, as seen in Table 2. Both criteria require fevers, clinical symptoms showing organ involvement, laboratory markers of inflammation, evidence of exposure to SARS-CoV-2 (positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen, or serology test, or likely contact with patients with COVID-19), and a ruling out of all other plausible diagnoses. Neither of the criteria provides definitive laboratory marker cutoffs, and only the CDC criteria provided additional timeline guidance requiring a minimum of 4 weeks from exposure to a (suspected or confirmed) COVID-19 case to the onset of symptoms.

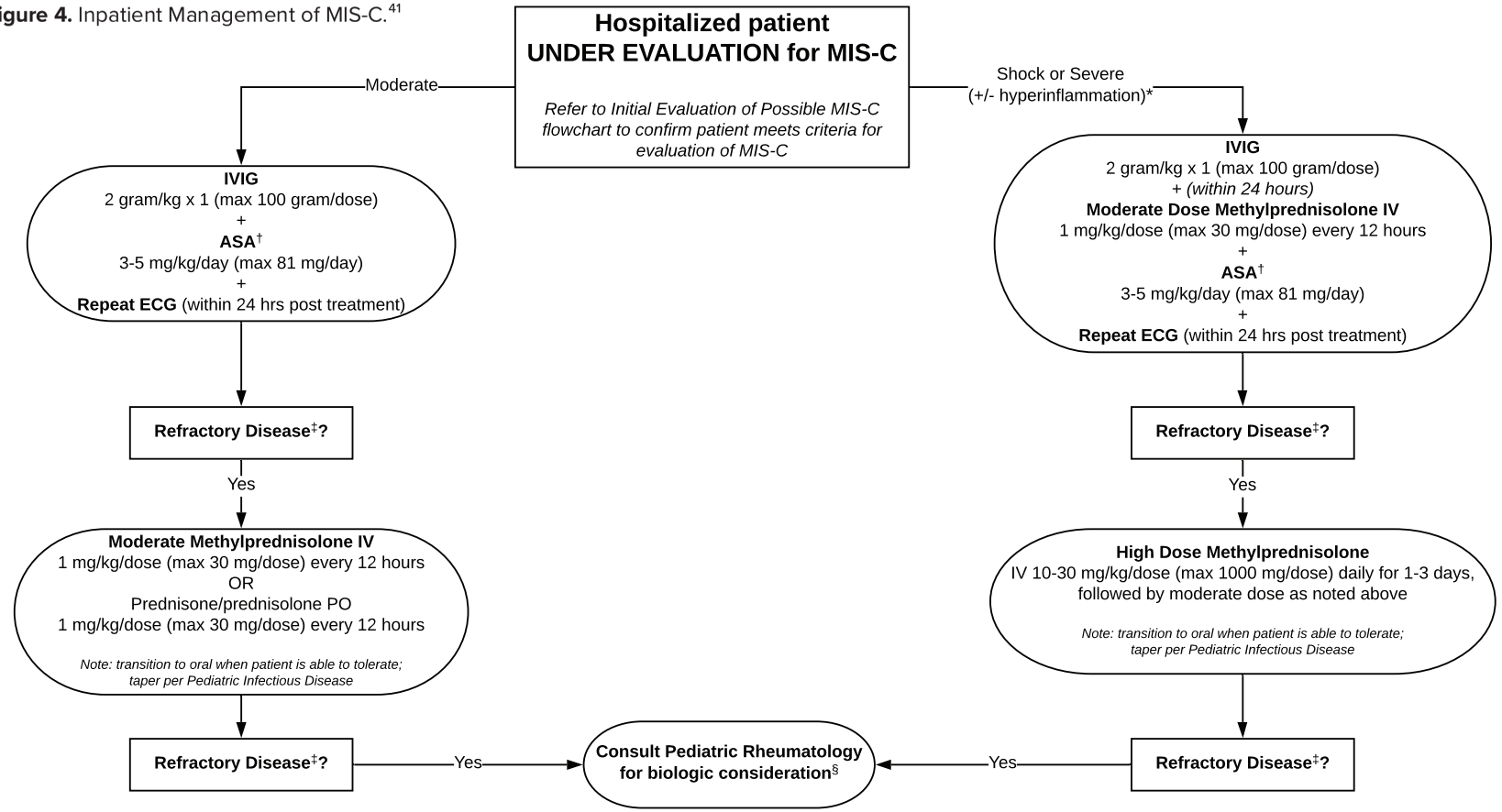
MIS-C Severity Definitions. Severity definitions currently do not exist, making the classification of severity exceedingly difficult. Institution-specific protocols shared among professionals are not well defined and can be subjective, but they have become the only source to meet this need. Factors to consider when distinguishing severity include organ injury, oxygen requirements, and hospital admission to the PICU (Table 3).[41,42]

Treatment

MIS-C's clinical profile ranges from clinically stable with normal or mildly depressed myocardial function to decompensated circulatory shock requiring vasoactive medications, invasive mechanical ventilation, and mechanical circulatory support.[20,24] Given the heterogeneity in disease severity, treatment goals for MIS-C patients include stabilizing patients with life-threatening manifestations (i.e., shock) and preventing long-term sequelae.[19] Long term sequelae include CAAs, myocardial fibrosis/scarring, and fixed cardiac conduction abnormalities.

Supportive Care. Supportive care therapies depend on the type and severity of the clinical manifestations.[43] Vital signs, hydration, electrolytes, and metabolic status must carefully be monitored. Patients presenting with shock should be stabilized with supportive care consisting of fluid resuscitation, inotrope support, and respiratory support, and in rare instances ECMO may be necessary in cardiovascular collapse.[43-45] Patients in shock should be resuscitated with volume expansion using buffered or balanced crystalloids; caution is warranted to avoid fluid overload due to elevated risk of severe myocardial dysfunction.[43,45] If hypotension is found to be fluid resistant, vasopressors should be initiated.[43] Epinephrine is recommended as first-line treatment for children, followed by norepinephrine if shock persists.[45] Antibiotics may be used in cases resembling severe bacterial sepsis but must be promptly discontinued when superimposed bacterial infections are excluded and cultures negative.[43] Immunomodulatory agents may not always be necessary, as Whittaker

Figure 4. Inpatient Management of MIS-C.[41]



ASA, aspirin; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram; ID, infectious disease; IV, intravenous; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome in children; PO, by mouth; SC, subcutaneous

* Hyperinflammation defined as:
- Evidence of myocardial dysfunction
- CRP > 15 mg/dL
- Ferritin > 1000 ng/m

† ASA = aspirin. Contraindicated in thrombocytopenia (platelets <30K) or active bleeding. Patients should be discharged with ASA; duration determined by cardiology. Refer to written guidelines for further details.

‡ Refractory disease could include any of the following:
- Persistent fevers > 24 hours post treatment
- Ferritin > 1000 ng/mL post treatment
- Worsening ECHO
- Peds ID discretion -if patient fails to improve

§ Severity of refractory disease:
- Moderate refractory disease: Anakinra 2 mg/kg/dose (max 100 mg/dose) SC once daily x 5 days
- Severe refractory disease: Anakinra 2 mg/kg/dose (max 100 mg/dose) SC every 6 hours on day 1, every 8 hours on day 2, every 12 hours on day 3, every 24 hours days 4-5

Table 4. Immunomodulatory Therapies[41]

Medication	Mild	Moderate	Severe/Shock
IVIG*	Supportive care only If clinically worsening, re-evaluate and consult Peds ID	2 gram/kg x 1 (max 100 gram/dose)	2 gram/kg x 1 (max 100 gram/dose)
Aspirin		3-5 mg/kg daily (max 81 mg/dose)	3-5 mg/kg daily (max 81 mg/dose)
Methylprednisolone *(Consider if severe refractory shock and/ or hyperinflammation)*		---	Moderate dose: 1-2 mg/kg/day (max 60 mg/day) divided every 8-12 hours
		If refractory† to IVIG and/or low dose steroids, proceed to the next therapeutic agent below	
Methylprednisolone		Moderate dose: 1-2 mg/kg/day (max 60 mg/day) divided every 8-12 hours	*(only if requiring multiple inotropes and/or vasopressors)* High dose: 10-30 mg/kg once daily (max 1000 mg/dose) x 1-3 days, followed by 2 mg/kg/day (max 60 mg/day) divided every 8-12 hours
		If refractory† to high-dose steroids, proceed to the next therapeutic agent below	
Anakinra		2 mg/kg/dose SC once daily (max 100 mg/dose) x 5 days	2 mg/kg/dose (max 100 mg/dose) SC every 6 hours day 1, every 8 hours day 2, every 12 hours day 3, every 24 hours day 4-5

ECHO, echocardiogram; ID, Infectious Diseases, IVIG, intravenous immunoglobulin; max, maximum; SC, subcutaneously

* Consider using ideal body weight if adolescent patient is morbidly obese; may consider maximum 100 g/dose in the setting of an IVIG shortage.

† Refractory defined as persistent fevers > 24 hours post steroids/IVIG AND ferritin >1000 –OR- worsening ECHO

et al[23] reported 22% of patients with MIS-C recovered with supportive care alone.

Pharmacologic Management. Initiation of pharmacologic treatment should depend on disease severity and patient clinical status.[19] Some patients with mild symptoms may only require close monitoring without any pharmacotherapy. Treatment regimens should be established by a collaborative multidisciplinary team including multiple subspecialties and a specialized clinical pharmacist.[19,23] However, patients with life-threatening presentations may benefit from early initiation of immunomodulatory treatment. A full diagnostic evaluation excluding all other potential diagnoses should be completed prior to initiating immunomodulatory therapies in order to prevent potential harm in patients who may not have MIS-C.[19]

With no available literature directly comparing therapeutic approaches, recommendations have been derived from firsthand experience managing MIS-C or extrapolated from guidelines treating similar pediatric conditions (i.e., KD, fulminant myocarditis).[19] Prospective and retrospective studies totaling 302 pediatric patients with MIS-C reported use of IVIG being the most commonly administered agent followed by glucocorticoids and biologics, with all 3 studies stating clinical improvement was noted for those treated.[1,9,46] Similar to the evaluation of MIS-C, the ACR guidelines recommend a stepwise progression of immunomodulatory therapies for the management of MIS-C using IVIG and/or glucocorticoids as the first line (Figure 4).[19] Glucocorticoids should be used as adjunctive therapy in severe disease or as intensification therapy in patients with refractory disease. Treatment response is determined based on the rapid resolution of fever.[18] Refractory disease is defined as persistent or recurrent fevers and/or significant end-organ involvement despite immunomodulatory treatment. With insufficient data comparing the efficacy of IVIG and glucocorticoids, these treatments may be used individually or as dual therapy to treat MIS-C.[19] Biologics may be considered as the last line of therapy in MIS-C patients with refractory disease despite IVIG and steroid treatments. The ACR also recommends low-dose aspirin (ASA) in all MIS-C patients without active bleeding or significant bleeding risk (Table 4).

Intravenous Immunoglobulin. IVIG is a blood product of normal IgG prepared from the serum of several thousand healthy donors.[47] The underlying mechanisms of IVIG for modulation of inflammation in acute KD has been suspected to include neutralization of conventional antigens or superantigens; however, the exact mechanism of action is not fully understood.[47,48] When used to treat patients with KD, the administration of IVIG was followed with noted reduction in cytokine levels, monocytes, macrophages, neutrophils, activated T cells, and changes in lymphocyte subsets, as well as an increase of NK cells.[18,48] Although IVIG's rapid anti-

inflammatory actions are beneficial, it is important to recall the most critical goal of treatment is to protect the vasculature and myocardium from immune-mediated damage.[48]

Intravenous immunoglobulin has been one of the most common immunomodulatory medications used in MIS-C patients to date and is currently considered the standard of care per the ACR MIS-C guidelines.[19,20,24] High-dose IVIG, dosed at 2 g/kg as a single dose, should be given to all MIS-C patients who are hospitalized and/or fulfill KD criteria.[19] Evidence for use of IVIG is based on the treatment of conditions similar to MIS-C inclusive of KD and fulminant myocarditis. In patients with KD, IVIG when initiated within 10 days of fever onset has been shown to reduce the risk of CAA from 25% to 4%.[29,49] Although the benefit of IVIG for the treatment of myocarditis remains highly controversial, there have been case reports of successful IVIG in coronavirus-associated myocarditis published.[19,50-55] Because KD mainly affects children younger than 6 years, treatment of MIS-C raises the concern of higher IVIG doses required by older children with higher body weight.[56] Multiple studies evaluating a single administration of medium-dose (1 g/kg/dose) versus high-dose (2 g/kg/dose) IVIG for treatment of KD support that moderate dosing could effectively alleviate clinical symptoms with no statistical difference in decreasing the incidence of CAA compared with high-dose IVIG.[56-59] However, most of these studies were retrospective and concluded that further clinical trials were needed to validate the results. A meta-analysis of 28 randomized controlled trials (n = 2596) found similar efficacy and safety between moderate-dose and high-dose IVIG for single use in the treatment of KD.[60] Both moderate-dose and high-dose IVIG showed no significant differences in the incidences of CAA in the acute phase ($p = 0.3$), subacute phase ($p = 0.14$), 6-month follow-up ($p = 0.95$), 12-month follow-up ($p = 0.74$), adverse reactions ($p = 0.74$), and resolution of fever within 2 days ($p = 0.18$). Given the earlier evidence supporting efficacy with moderate dosing, many institutions have maximized their daily IVIG dose for MIS-C treatment at 100 g per dose.[41,42,61,62] Although there is no evidence recommending an absolute maximum daily dose of IVIG, the higher doses required in larger patients contribute a significant volume load, which many patients cannot tolerate. Until further studies are available, the moderate-dose versus high-dose IVIG debate will continue. Pending results from the phase 3 RCT evaluating 1 g/kg once versus 1 g/kg twice versus 2 g/kg will hopefully provide answers to this long-anticipated debate (NCT 02439996).

The ACR guidelines recommend using ideal body weight (IBW) for IVIG dosing.[19] Ideal body weight is defined as being a reflection of lean body mass and is particularly important with the increasing rate of obesity in pediatric patients.[63] Miscalculations of medications can lead to lack of efficacy if subtherapeutic or toxicity if supratherapeutic. Kang et al[63] ultimately concluded that various methods to calculate pediatric IBW lead to differences of varying statistical and clinical significance, and larger sample sizes are needed in order to determine the most accurate method for specific subgroups of varying age and height percentiles. Hence, it may be appropriate to consider using IBW or adjusted body weight for adolescents who are obese, defined as body mass index >30 kg/m^2, because using total body weight (TBW) may result in supratherapeutic dosing and increase the risk for adverse drug reactions (ADRs). However, in non-obese pediatric patients, dosing of IVIG should be based on TBW until there is evidence otherwise. Unlike KD, a second dose of IVIG is not recommended in refractory MIS-C given the risk of volume overload and adverse reactions, such as hemolytic anemia, associated with large doses of IVIG.[19]

Overall, IVIG is typically well tolerated and considered relatively safe.[65] The incidence of ADRs has been reported to range widely from 1% to 81% of patients or courses or infusions.[63] Immediate events include transient flu-like symptoms, hypotension, tachycardia, and anaphylaxis reactions that can be managed by administration of fluids, reducing the IVIG infusion rate, changing to another preparation of IVIG, or premedication. Pharmacotherapies for premedication include analgesics, non-steroidal anti-inflammatory drugs, antihistamine, or intravenous glucocorticoids. Late ADRs, although rare, include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia, rash, pseudohyponatremia, autoimmune hemolytic anemia, and pulmonary complications. Respiratory complications have been reported and are usually attributed to fluid overload or to allergic or vasomotor reactions.[65,66] Prior to IVIG administration, cardiac function and fluid status should be assessed to evaluate risks for volume overload.[19] Methods to avoid IVIG volume overload include decreasing the rate of IVIG by extending the infusion time (i.e., infuse over 12 hours) or by dividing the total treatment dose of 2 g/kg to 1 g/kg for 2 doses given over 2 days. Otherwise, pulmonary edema and increased pro-BNP levels may require treatment with diuretics.[18,19] Live vaccines (e.g., MMR and varicella vaccines) should be administered at least 8 months after administration of IVIG as the efficacy of the live vaccines will be decreased if given before that time.[67] If a live vaccine was administered within 14 days prior to IVIG, it should be repeated 8 months after IVIG.

Aspirin. There have been reports of deep vein thrombosis (1%) or pulmonary embolisms (7%) in US patients with MIS-C.[68] Marked abnormalities in the coagulation cascade (i.e., prominent elevations in D-dimer and fibrinogen) reported in patients with MIS-C raise concerns of increased risks of thrombosis.[4,19,69] Because KD is an acute systemic vasculitis in children, antiplatelets are commonly used to attenuate vasculitis and prevent thromboembolisms.[70]

Salicylate, an active ingredient of ASA, has anti-inflammatory (at high doses), antipyretic, and antiplatelet properties (at low doses) by inhibiting cyclooxygenase (COX) enzyme, which in turn inhibits production of lipid mediators (thromboxane, prostacyclin, and prostaglandin).[18,29] For patients with acute-phase KD, guidelines suggest administration of high-dose (80–100 mg/kg/day) or moderate-dose (30–50 mg/kg/day) ASA, with a maximum daily dose of 4 grams, until the patient is afebrile with no effect on CAA at follow-up.[29] Although ASA may help to shorten the fever duration, a systemic review revealed insufficient evidence for the effectiveness of antiplatelet therapy for KD.[70,71] A meta-analysis of 6 studies (n = 11,103) showed no difference between low-dose (3–5 mg/kg/day) and high-dose (≥30 mg/kg/day) ASA in the incidence of CAA (relative risk [RR], 0.85; 95% confidence interval [CI], 0.63–1.14; p = 0.28), the risk of IVIG-resistant KD (RR, 1.39; 95% CI, 1.00–1.93; p = 0.05), or the duration of fever and hospitalization (mean SD, 0.03; 95% CI, −0.16 to 0.22; p = 0.78).[72] Given the lack of evidence supporting ASA's role in reducing the frequency of CAA, doses exceeding low-dose ASA for the treatment of MIS-C are typically not recommended.

Current guideline recommends low-dose ASA (3–5 mg/kg/day; maximum 81 mg/day) in all MIS-C patients requiring IVIG.[19] Low-dose ASA should be continued until platelet counts normalize and there are normal coronary arteries at ≥4 weeks after diagnosis is confirmed. Treatment with ASA should be avoided in patients with active bleeding, significant bleeding, and/or thrombocytopenia (platelet count less than or equal to 80,000/μL).

Low-dose ASA therapy is used for antiplatelet effects and has not been associated with the development of Reye syndrome.[29] Alternative antipyretics drugs (i.e., acetaminophen) may be considered as needed for fever in patients who may have concurrent influenza infection. In patients with both influenza and MIS-C, an alternative antiplatelet agent should be considered for a minimum of 2 weeks. Alternative antiplatelet agents include oral clopidogrel 0.2 mg/kg/day (maximum 75 mg/dose) once daily or dipyridamole 2 to 6 mg/kg/day given in 3 divided doses (max 100 mg/dose).[58,73] Of note, concomitant use of ibuprofen should be avoided in pediatric patients with CAA because it can antagonize the irreversible platelet inhibition induced by ASA.[29]

Corticosteroids. Corticosteroids are effective in a broad range of vasculitis and other inflammatory conditions through the inhibition of prostaglandins and other inflammatory cytokines, thus suppressing fever and inflammation.[49] Corticosteroids have 2 groups of action: glucocorticoid and mineralocorticoid effects.[74] Corticosteroids with glucocorticoid activity affect metabolic changes and anti-inflammatory effects, whereas mineralocorticoid effects affect loss of potassium/hydrogen as well as retention of salt/water. Pharmacotherapy agents with glucocorticoid activity in descending order include dexamethasone, methylprednisolone, and prednisone.[74,75] Considerations of the dosage formulation and half-life of the drug should be considered when choosing an agent.

Patients may not always respond to first-line MIS-C pharmacotherapies. Approximately 15% to 20% of patients with KD remain refractory even after the completion of IVIG, and such patients are 4 times more likely to develop CAA compared with complete responders.[76,77] That being said, the exact incidence of refractory MIS-C remains unknown. However, if similar to KD, this group of MIS-C non-responders may likely be at high risk for development of CAA. Glucocorticoids in combination with IVIG as initial treatment for KD have been shown to reduce the rate of CAA, lower coronary artery Z-scores, lower CRP levels, and rapidly resolve fever.[29]

According to the ACR MIS-C guidelines, glucocorticoids should be used as adjunctive therapy in patients with severe disease or as intensification therapy in patients with refractory disease.[19] To date, for the treatment of MIS-C no specific glucocorticoid has been identified as the recommended agent, given none have been found to be superior when appropriately dosed. Additionally, glucocorticoids may be added to IVIG as first-line therapy in patients without shock or severe end organ involvement but who present with concerning features, such as ill appearance, high elevated BNP, or unexplained tachycardia. In patients with shock and/or organ-threatening disease, low- to moderate-dose glucocorticoids (e.g., methylprednisolone IV 1–2 mg/kg/day divided in 2–3 doses) should be used as adjunctive therapy with IVIG. A retrospective study of 96 pediatric patients with MIS-C compared IVIG with methylprednisolone to IVIG alone because initial therapy reported the combination treatment was associated with a more favorable fever course.[78] After propensity score matching, treatment with IVIG/methylprednisolone was associated with a lower risk of treatment failure compared with IVIG alone (adjusted RR, −0.28; 95% CI, −0.48 to −0.08; odds ratio [OR], 0.25; 95% CI, 0.09–0.7; p = 0.008). The combination treatment group was also significantly associated with lower risk of use of second-line therapy (ARR, −0.22; 95% CI, −0.4 to −0.04; OR, 0.19; 95% CI, 0.06–0.61; p = 0.004), hemodynamic support (ARR, −0.17; 95% CI, −0.34 to −0.004; OR, 0.21; 95% CI, 0.06 – 0.76), acute left ventricular dysfunction occurring after initial therapy (ARR, −0.18; 95% CI, −0.35 to −0.01; OR, 0.2; 95% CI, 0.06–0.66), and duration of stay in the PICU (median, 4 vs 6 days).

Patients refractory to IVIG and low- to moderate-dose glucocorticoids, especially those with life-threatening complications or requiring high-dose or multiple inotropes and/or vasopressors, high-dose IV pulse glucocorticoids (e.g., methylprednisolone IV 10–30 mg/kg/day once daily) may be considered for 1 to 3 days.[19] Intravenous corticosteroids should be converted to oral

Table 5. Anakinra Dosing

Severity	Route	Dose*		Comments
Moderate	SC	CrCl ≥30 mL/min: 2 mg/kg/dose daily or every 12 hr	CrCl ≤30 mL/min: Reduce frequency (i.e., every 12 hr to daily or daily to every other day)	If poor response, may increase to every 6–8 hr
Severe	IV push	CrCl >30 mL/min: 2 mg/kg/dose every 6 hr	CrCl <30 mL/min: 2 mg/kg/dose every 8–12 hr	Administer as slow IV push over 3–5 min

CrCl, creatinine clearance
* Typical maximum 100 mg/dose. Taper over 2–3 weeks.

once the patient is able to tolerate them. An example corticosteroid course may include intravenous methylprednisolone 10 to 30 mg/kg/dose (maximum 1000 mg/dose) given once daily for 1 to 3 days, followed by oral prednisolone 2 mg/kg/day (maximum 60 mg/day) divided every 8 to 12 hours until day 7 or until CRP normalizes.[19,79]

Short-course corticosteroid therapy (less than 7 days) generally does not require tapering upon discontinuation. Longer courses, regardless of dose, require a taper over at least 2 weeks to avoid rebound inflammation.[79] Methods for tapering steroids vary widely, as does the duration, and no method has been deemed superior. One method of tapering includes decreasing oral prednisolone to 1 mg/kg/day (maximum 30 mg/day) for 2 weeks, then 0.5 mg/kg/day for 2 weeks, then taper by 5 mg every week (down to daily dose of 10 mg daily), then by 2.5 mg every week until off.[19] However, in children where the earlier method is not applicable (e.g., weighing less than 10 kg), an alternative method of tapering is weaning by 20% of the dose the first week, and then 10% each week thereafter, with a quicker wean if the patient tolerates. Corticosteroid use is not novel in the treatment of MIS-C.[20,24] The decision to use steroids should be a multidisciplinary team approach where benefit must outweigh the risk. Dexamethasone has been the most widely studied corticosteroid used for the treatment of acute COVID-19 (see part 1 of our trilogy for further information).[10] Other steroids, such as methylprednisolone or prednisolone, have become extensively used for MIS-C.[45] Prospective clinical trials are needed to establish the role of steroids in MIS-C and identify optimal agents and doses.

Like with all medications, the use of corticosteroids is not without side effects. The risk of side effects depends on the dose and length of treatment, as well as other concurrent medical comorbidities.[74] Short-term side effects include increased appetite, weight gain, fluid retention, gastritis, headaches, mood swings, elevated blood glucose, hypertension, and glaucoma. Patients on high-dose steroids should receive concurrent stress ulcer prophylaxis. Long-term side effects include suppressed immunity, increased susceptibility to infections, increased cholesterol levels, weight gain, osteoporosis, deposition of body fat, thinning of skin, cataracts, stunting, and hypothalamic pituitary axis suppression.

Biologics. The use of biologic therapy as an additional immunomodulator should only be considered in patients refractory to corticosteroid and IVIG treatment or those with severe, life-threatening MIS-C manifestations.[19] Critically ill patients and those who have features of MAS are defined as severe MIS-C.[19] Refractory MIS-C is defined as patients who have failed to respond or have contraindications to IVIG and/or corticosteroid.[19]

Based on the known underlying pathophysiology of MIS-C, biologic therapy targeting IL-1 has the most potential, and initial results show promise.[19] Biologic therapies are more expensive, and although they are routinely used in children for other disease states, extended long-term outcomes are lacking.[80] Treatment with biologics should only be initiated if the potential benefits outweigh the risks.[19] Biologic agent selection and use may also be limited secondary to drug availability stemming from nationwide backorder and/or influenced by institution-specific formularies.

Anakinra. Anakinra is a recombinant human interleukin-1 receptor antagonist (IL-1Ra) that blocks IL-1α and IL-1β and competitively inhibits IL-1R1 binding.[81] Anakinra is FDA approved for the treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. Anakinra is frequently used as off label treatment for multiple inflammatory syndromes, including familial Mediterranean fever, refractory pericarditis, MAS, hemophagocytic lymphohistiocytosis (HLH), refractory KD, and other cytokine storm syndromes.[80] To date, anakinra has been the most widely used biologic in the treatment of MIS-C.[19,79]

Selecting a biologic therapy with the potential to achieve rapid serum concentrations and provide rapid onset is critical. Case and cohort studies using anakinra for the treatment of COVID-19–associated acute respiratory distress syndrome began surfacing in late April 2020 describing clinical improvements in the absence of significant side effects.[17] The doses, administration routes, and treatment durations vastly varied and were dependent on patient age, severity, comorbidities, and/or geographic location. Anakinra possesses a

short half-life (4–6 hours), large therapeutic window, rapid onset, and a relatively good safety profile (e.g., less hepatotoxicity and myelosuppression) compared with other biologics (i.e., tocilizumab).[80] Secondary to this favorable profile, anakinra has become preferred to tocilizumab for the treatment of MIS-C. In addition, anakinra has already been FDA approved in pediatrics, and use is well-established in other inflammatory syndromes.[17] As KD and MIS-C share many similarities, it is no surprise that anakinra has been used to treat both IVIG refractory KD and MIS-C patients.[82]

Supplied as prefilled syringes (100 mg/0.67 mL), anakinra is typically administered SC in the absence of any significant concerns or contraindications.[81] Specific to MIS-C, the ACR recommends anakinra doses to be at least 4 mg/kg/day IV or SC.[19] The ACR does not provide recommendations regarding treatment duration or dosing intervals, nor does it designate a preferred route of administration. Driven primarily by indication and provider practices, pediatric anakinra doses range widely from 2 to 10 mg/kg/day administered in divided doses. The typical anakinra max dose is 100 mg per dose.[17,19,80] Dosing intervals range from continuous to every 6 hours to once daily. Dose and interval selection is specific to indication and route of administration (Table 5).[17,19,80,81]

Subcutaneously administered anakinra should be used in most patients with MIS-C, who are clinically stable and without contraindication to SC therapy.[19] Subcutaneous anakinra does not require dosage form manipulation and is longer acting, allowing less frequent dosing, which simplifies the regimen. The use of IV anakinra should only be considered in unstable patients where a rapid onset is critical and/or in patients with significant thrombocytopenia, severe edema, and/or with severe skin manifestations.[80] Although more is required to ensure safe dose preparation and dosing must be multiple times daily, the shorter half-life of IV anakinra allows for the faster obtainment of serum concentrations and a more rapid onset.

The use of IV anakinra has been studied in adult sepsis and pediatric secondary HLH, and has gained support for the treatment of HLH and MAS.[80,83,84] By means of extrapolation, IV anakinra became of particular interest for the treatment of severe MIS-C.[80,84] MIS-C patients commonly present with significant thrombocytopenia, skin rashes, and edema, which are known to increase injection site risks and further prolong drug absorption.[80] Upon direct comparison, IV anakinra appears to be superior to SC. Intravenous anakinra is capable of achieving maximum plasma concentration much more rapidly and reported to be 25 times greater than that of SC, therefore potentially improving efficacy and outcomes. However, this must be interpreted with caution because this is only theoretical and has yet to be proven in head-to-head clinical trials. As clinicians, it is imperative to understand the pharmacokinetic differences and their clinical relevance with the following questions in mind: Do elevated plasma concentrations correlate with improved efficacy? Are the elevated plasma concentrations associated with more significant adverse events? Do these alternations in pharmacokinetic parameters necessitate alternative dosage regimens or dose adjustments?

Although not easily achieved, anakinra is capable of crossing the blood-brain barrier.[80] Higher plasma concentrations are required to achieve cerebrospinal fluid penetration; therefore, IV administration is the ideal route if patients are experiencing neurologic MIS-C manifestations. Given the paucity of evidence in the treatment MIS-C–related neurologic symptoms, this assumption is primarily anecdotal. The use of IV anakinra may be further complicated because of a lack of data on appropriate methods of drug preparation, stability, and administration. To ensure rapid drug effect and minimize discomfort related to medication administration, IV anakinra can be given undiluted as a slow IV push over 1 to 5 minutes via a dedicated line; however, it does require syringe manipulation and/or further dilution.[80,82] Unfortunately, anakinra lacks stability data outside its original syringe in addition to diluent compatibility overall, which complicates the overall picture in critically ill patients on multiple continuous infusions.[81]

If anakinra is administered via IV and product manipulation is required, this should occur in a sterile environment. For IV anakinra, the practice of assigning beyond use dates to ensure sterility and stability has been highly debated and varies between studies and institutions. Upon review of publications and observations of practice the assigned beyond use dates ranged from 1 hour to a maximum of 8 hours.[85] A study conducted by Monteagudo et al[86] describes further diluting the patient-specific anakinra dose with 0.9% sodium chloride to a final concentration of 1 to 5 mg/mL as their pharmacy protocol for continuous anakinra infusion. The final bag of diluted anakinra was protected from light, dated, and assigned an 8-hour expiration date.[85,86]

Anakinra clearance appears to be unaffected by changes in the route of administration.[80] Anakinra is predominantly cleared renally as the plasma clearance decreases with decreasing renal function.[87] Mean plasma clearance in patients with mild (creatinine clearance [CrCl] 50–80 mL/min), moderate (CrCl 30–49 mL/min), severe (CrCl <30 mL/min), and end-stage renal disease was decreased by 16%, 50%, 70%, and 75%, respectively.[81,88] Dialysis has minimal effects on the removal of anakinra because less than 2.5% of the dose administered was removed.[87] The short half-life of anakinra is prolonged to approximately 7 hours and 10 hours in those with severe renal impairment (CrCl <30 mL/min) and end-stage renal disease, respectively. Although pharmacokinetic data are available for children with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndrome, studies only evaluated

appropriate dosing with no assessment of how half-life elimination is affected with renal function.[89] However, because anakinra is eliminated primarily renally, it may be reasonable to reduce the frequency of anakinra administration when pediatric patients have severe renal impairment.

Anakinra is generally well tolerated; however, rare but potentially serious adverse effects have occurred.[81] As with many biologics, anakinra has been linked to increased infection risks and should not be initiated in patients with an active concurrent infection. Additional risks include anaphylaxis, neutropenia, and eosinophilia. Increased serum transaminases may occur and should be monitored carefully at baseline and for the duration of therapy. Anakinra-induced hepatic injury is usually self-limiting and resolves within a few weeks of discontinuation, although there are cases of hepatic failure that have been reported in adolescents.[81,90] Anakinra should not be used in combination with additional biologic immunosuppressant therapies.[81] Live vaccinations should not be administered while receiving anakinra.

Anakinra treatment duration should be individually tailored depending on clinical course.[19] A slow taper over 3 weeks is recommended to mitigate the risk of inflammatory rebound when discontinued, and an abrupt cessation of therapy should be avoided.[19,80] If using IV anakinra, once frequency has been tapered (e.g. every 6 or 8 hours to every 12 hours), the route should be transitioned to SC as this route mitigates serum level fluctuations and the risk of rebound given the longer half-life. As with much of the published data in COVID-19 treatment and now MIS-C, additional larger randomized controlled trials are necessary for confirmation of conclusions.[17] Until then, clinicians should individualize therapy for each patient by cautiously balancing effectiveness while simultaneously mitigating risks.[80]

Tocilizumab. Tocilizumab, an IL-6 inhibitor, has been used to mitigate the cytokine storm associated with SARS-CoV-2 in both pediatric and adult patients.[91-93] Given the association between IL-6 levels and negative outcomes in COVID-19, IL-6 neutralization with tocilizumab has been appealing.[10,19] However, IL-6 levels in MIS-C seem to be lower than compared with SARS-CoV-2 infection in adults.[91,94] Large studies for use of tocilizumab in treatment of MIS-C yielded successful control of inflammation but lack data on the outcome of CAA.[1,9,91] There is a significant concern in children with KD treated with tocilizumab for putative worsening of CAA.[91,95] Additionally, the effects of tocilizumab are long-lasting, leaving little recourse if a patient does not respond favorably to the medication.[19]

Infliximab. Infliximab is a chimeric monoclonal antibody that binds to TNF-α, thereby interfering with induction of proinflammatory cytokines.[96] Although infliximab has been described in the literature to treat MIS-C, particularly patients with inflammatory bowel disease, such treatments were not routinely used in clinical practice nor recommended by ACR.[19,97] The role of anti-TNF agents in patients with MIS-C temporally related to COVID-19 requires further investigation.[97]

Prevention.

There are no known methods to prevent MIS-C. However, there are some considerations to reduce the risk of contracting SARS-CoV-2.

Non-pharmacotherapy. Caregivers and patients should continue to take all precautions in order to prevent children from contracting SARS-CoV-2.[98] These measures include scrupulous handwashing, social distancing, and appropriate coverage of nose and mouth with face masking. Please refer to part 1 of our trilogy for more detailed information regarding non-pharmacotherapy prevention strategies.[10]

SARS-CoV-2 Vaccines. All qualified individuals, pediatric patients, and caregivers should receive the safe and effective SARS-CoV-2 vaccine if there are no contraindications.[99] In the United States, COVID-19 mRNA vaccines have been found to be 90% to 95% effective, whereas vector vaccines are 74% effective 2 weeks after vaccination.[100-102] Vector vaccines contain a modified version of a different virus than the one that causes COVID-19.[99] Once the viral vaccine enters the human cell, the genetic material instructs the cell to make copies of a unique COVID-19 protein, prompting the body to build T lymphocytes and B lymphocytes imperative to recognize and fight the virus. The current Emergency Use Authorization–approved COVID-19 vector vaccine only requires 1 shot, an advantage versus mRNA vaccines. Studies are ongoing in children at present down to age 5 years, with more planned. Please refer to part 1 of our trilogy series for more detailed information regarding the SARS-CoV-2 vaccine.[10]

Receipt of the SARS-CoV-2 vaccine does not result in positive nucleic acid amplification tests or antigen test results.[103] SARS-CoV-2 antibody tests that detect the responses to the spike protein may become positive following vaccination, whereas nucleocapsid protein would not. To date, antibody testing is not recommended to determine immunity to COVID-19 following vaccination or to assess the need for vaccination.[103]

Antiplatelet and Anticoagulation Considerations. Patients with MIS-C may be at increased risk for developing thrombosis, especially if patients also present with or develop severe ventricular dysfunction or CAAs.[104] There have been reports of deep vein thrombosis or pulmonary embolisms in pediatric patients with MIS-C.[66] Antiplatelet therapy should be considered for all patients who meet the KD criteria, have coronary artery changes, or have other risk factors for thrombosis.[19,104] Therapeutic anticoagulation is strongly recommended for all patients with severe ventricular dysfunction, large CAAs, or additional independent risk factors. For all patients not described previously,

antithrombotic therapies should be individually tailored depending on a risk and benefit assessment. Please refer to the upcoming part 3 of our trilogy series for a more in-depth and critical evaluation of antiplatelet and anticoagulation considerations in acute COVID-19 and MIS-C in pediatric patients.

Follow-up. All patients with MIS-C should have follow-up appointments with pediatric infectious diseases and pediatric cardiology specialists.[19] Follow-up appointments with rheumatology specialists should be determined on a case-by-cases basis. However, if a patient is discharged on a steroid taper, management of that taper should be overseen by a licensed provider. During the active disease course, because arrhythmias and heart block may occur, electrocardiograms should be monitored every 24 to 48 hours with daily BNP and troponin (if baseline testing was found to be abnormal) and repeat ECHOs as clinically indicated to reassess the coronary arteries.[19,104] For patients with coronary artery changes, ECHOs should be repeated every 2 to 3 days until coronary artery size is stable; this may be daily if clinically indicated. Once patients are discharged, all MIS-C patients should have a repeated ECHOs at 1 to 2 weeks with repeat BNP and/or troponin labs if not normalized at discharge. All patients should be considered for Holter monitor if any conduction delays or ectopy during the acute phase was noted or if abnormal electrocardiogram at a follow-up visit. Echocardiogram and/or electrocardiograms may need to be repeated depending on the clinical spectrum of MIS-C. Because coronary artery involvement may develop in the convalescent phase, all patients with MIS-C should have a follow-up ECHOs and/or electrocardiogram in 4 to 6 weeks, with various further follow-ups, depending on the clinical spectrum of MIS-C.

Conclusion

MIS-C is a hyperinflammatory syndrome with a wide range in severity presentation. The most common clinical symptoms include gastrointestinal symptoms, persistent fevers, and cardiac manifestations. Current treatments of MIS-C have been derived from previous experience in the treatment of KD with immunomodulatory agents. A tiered and multidisciplinary approach involving multiple pediatric specialists should be used to guide individualized treatment in the evaluation and management of patients who meet the definition for MIS-C and is crucial for successful outcomes. These recommendations are subject to change as our understanding of pediatric SARS-CoV-2 infection continues to evolve and higher quality evidence become available.

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