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Multisystem Inflammatory Syndrome in Children: A Comprehensive Review Over the Past Five Years

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Abstract

Multisystem Inflammatory Syndrome in Children: A Comprehensive Review over the Past Five Years This review explores many facets of Multisystem Inflammatory Syndrome in Children (MIS-C) over the previous 5 years. In the time since the COVID 19 pandemic gripped our medical systems, we can now explore the data that has been collected from the previous years. The literature has allowed us to better understand the impact of COVID 19 and the post illness occurrence of a severe systemic inflammatory disease on our youngest patient populations. This paper will outline the pathophysiology of MIS-C, the treatments utilized, short and long-term patient outcomes including epidemiological factors.

Keywords

COVID-19, MIS-C, Multisystem Inflammatory Syndrome, SARS-CoV2, inflammation, Neutrophils, IVIG, glucocorticoids, Cardiac, Immune dysregulation, pediatrics, critical care, intensive care unit, outcomes

Introduction

In late April 2020, several months after the onset of the COVID-19 pandemic, there were reports from different countries of children who became critically ill with a severe systemic inflammatory disease, presenting with an unusually high rate of myocarditis, shock, and a high prevalence of abdominal symptoms..[1–10] This disease is now known as multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). MIS-C generally presents 2–6 weeks after acute COVID-19, and is characterized by fever, multi-organ dysfunction, and laboratory evidence of severe inflammation. Fever, nausea, vomiting, and abdominal pain are common symptoms, and cardiovascular involvement including myocarditis, decreased ventricular function, and coronary artery aneurysms are often reported in patients hospitalized with MIS-C. During the peak of disease severity, 75% to 80% of the patients were admitted to the ICU; 40–60% required vasoactive support and 10–20% required invasive mechanical ventilation.[11,12] The diagnostic criteria used by the World Health Organization (https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19) and the Centers for Disease Control (https://ndc.services.cdc.gov/case-definitions/multisystem-inflammatory-syndrome-in-children-mis-c/) both require the presence of fever at least 24 h prior to diagnosis, multiorgan involvement, elevation of inflammatory markers, evidence of a recent COVID-19 infection, and exclusion of other possible etiologies.[13,14] In 2023, the CDC

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case definition was updated to utilize more specific diagnostic criteria and to reduce misclassification with other pediatric inflammatory conditions.

MIS-C Pathology and Pathophysiology

MIS-C symptoms and pathophysiology share features with several hyper-inflammatory diseases—Kawasaki disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS). When MIS-C surfaced as an unknown disease, it was initially thought to be a variant of KD but is now recognized to be a distinct illness.[15] KD tends to occur in children aged 6 months to 5 years with a slight male predominance and a higher incidence in children of Asian descent; MIS-C tends to occur in patients over 6 years old, without a gender predominance. Myocardial inflammation, cardiac dysfunction and cardiogenic shock are more

common in MIS-C; coronary dilatation and aneurysms are more often common in KD. Gastrointestinal and respiratory manifestations are more prevalent in MIS-C. The immunologic response to KD and to MIS-C share similarities, with a greater degree of systemic inflammation and organ involvement in MIS-C.[15]

Neutrophil Activation

Neutrophil activity is a key contributor to the hyper-inflammation and immune dysregulation which are hallmarks of MIS-C. Boribong et al[16] report that neutrophil activation in MIS-C results in gene expression profiles that resemble those in sepsis and acute respiratory distress syndrome (ARDS), with a predominantly granulocytic myeloid-derived monocyte cell signature. The most highly upregulated genes are those involved in neutrophil activation and in reactive oxygen species production; the most highly enriched pathways coincide with those seen in neutrophils of adult ARDS patients. Additional upregulated pathways involve active metabolic processes, such as oxidative phosphorylation, glycolysis, and mTORC1 signaling, as well as pathways involved in tissue damage, including neutrophil degranulation, tumor necrosis factor-α (TNF-α) signaling, and interleukin-1 (IL-1) signaling. The neutrophil pathways that are activated in MIS-C differ from those in pediatric acute COVID-19, which is characterized by anti-viral interferon-mediated pathways, with highly upregulated genes being those involved in neutrophil activation, recruitment, and chemotaxis,[16–30] As expected, there is also an increased expression in particular, TNF-α, IL-1, and IL-6.[16–18]

Neutrophil-Extracellular Trap (NET) Formation

While neutrophils are essential in the defense against infectious agents, an overly exuberant neutrophil response can be harmful to the host. Formation of neutrophil-extracellular traps (NETs) is an example and contributes to the pathogenesis of adult COVID-19.[19–23] It has also been implicated in MIS-C, with a current hypothesis suggesting[16] that SARS-CoV-2 antigen: antibody immune complexes, formed during acute COVID-19 infection, become a trigger for NET formation when these patients subsequently develop MIS-C. Testing this theory in in-vitro experiments, Boribong et al[16] showed that addition of Spike protein to convalescent plasma from pediatric COVID-19 patients induced NET formation, but not when added to plasma from control patients. As part of an international study, Carmona-Rivera et al[23] detected elevated levels of NET remnants in the blood of patients with MIS-C and those with chilblain-like COVID skin lesions (CLL) in a cohort of MIS-C patients from Chile. The level of degraded NET products was associated with disease severity, including symptoms of respiratory compromise, shock, and cardiac dysfunction. In contrast to patients with MIS-C, pediatric patients with mild acute COVID-19 infection do not exhibit extensive NET formation.[24] These data suggest that NETs do play a role in the pathogenesis of MIS-C.

T-Lymphocyte Activation

Activation of T-lymphocytes constitute another cellular response that adds to the hyper-inflammatory state in MIS-C. Porritt et al[25] found an expansion of T cells expressing the T-cell receptor (TCR) beta variable gene 11e2 (TRBV11-2), encoding Vbeta (Vb) 21.3 in many patients with severe MIS-C. These TRBV11-2-positive polyclonal T cells are active in cell adhesion, activation, and the mitochondrial pathway of apoptosis. This clonal expansion can be extensive, with TRBV11-2 T cells forming as much as 24% of clonal T cells. The extent of this expansion correlated with MIS-C severity and serum cytokine levels, and the frequency of TRBV11-2 clones decreased along with levels of MIS-C biomarkers within 1-2 weeks after glucocorticoid administration. Other T-cell clonal expansions have also been reported in MIS-C.[26–28] Ramaswamy et al report that T and B cell clonal expansion, as well as cytotoxic gene expression in CD8+ T cells, appear to be associated with MIS-C severity.[29]

The discovery of T cell clonal expansion, along with similar manifestations of shock in MIS-C and in Toxic Shock Syndrome (TSS), stimulated a search for an epitope on SARS-CoV-2 that may have structural similarities to the Staphylococcus enterotoxin superantigen, which elicits a powerful immune response even at low antigen concentrations.[30] It does so by binding to class II MHC molecules on T lymphocytes with high affinity, resulting in the proliferation of T cells expressing the TcR-VB (T cell receptor-β chain variable region) gene products. Using computational models, Noval Rivas et al[31] identified an epitope on the SARS-CoV-2 spike glycoprotein that binds T-cell receptors with high affinity and that shares similarities with the sequences and structure of Staphylococcal enterotoxin. This epitope has not been found in the spike proteins of other beta-coronaviruses besides SARS-CoV-2. The discovery lends support to the super-antigen hypothesis of MIS-C pathophysiology.[31] Consistent with this theory, pre-treatment with a monoclonal antibody to the Staphylococcus enterotoxin in cell culture experiments blocks entry of SARS-CoV-2 into cells in a concentration-dependent

manner.[32] Several HLA classes have been associated with severe MIS-C in children who demonstrate TRBV11-2 skewing, raising the question as to whether genetic predispositions to severe MIS-C may be linked to specific T-cell clonal expansions.[25] Noval Rivas et al report that the superantigen-like motif in SARS-CoV-2 shares homologies with α-neurotoxin from snake venom and with neurotoxin-like regions from rabies virus strains, with conjectures regarding a possible link to the neurological symptoms seen in MIS-C, such as headache, lethargy, and confusion.[31]

Antibody-Dependent Enhancement

Antibody-dependent enhancement (ADE) is a process that has been proposed as another mechanism which induces the exaggerated inflammatory response in MIS-C.[33] In ADE, antibodies that did not fully neutralize the virus could instead enhance virus dissemination.[34] An analogous situation is recognized in severe Dengue fever,[14] and ADE is an important consideration in vaccine development.[35,36] Support for the ADE theory of MIS-C pathogenesis comes from the observation that children with MIS-C have higher antibody titers to Spike protein than children with acute COVID-19 infection without progression to MIS-C,[35,37] and that higher IgG antibody levels are associated with greater severity of illness in SARS-CoV-1 infection. Wan et al[33] proposed a model in which antibody binding to viral Spike protein and to the IgG-Fc receptor is a process which facilitates viral entry into the cell through canonical viral-receptor dependent pathways.[33]

Neutrophil to Lymphocyte Ratio as a Biomarkers for MIS-C Disease Severity

As leukocytes undergo changes with acute COVID-19 infection and with MIS-C, leukocyte population parameters, such as the neutrophil-lymphocyte ratio (NLR), may serve as biomarkers for MIS-C diagnosis and disease severity.[22,30,38] Gullu et al[11] analyzed the utility of several laboratory indices in 374 pediatric patients (292 COVID-19 PCR-positive,12 MIS-C,70 healthy controls) and reported that the NRL, along with pro-BNP, CKMB, and troponin-I values were all helpful in diagnosing and predicting disease severity of MIS-C. Kane et al[38] examined the use of monocyte anisocytosis as another potential biomarker of SARS-CoV-2 disease severity. Monocyte anisocytosis is a measure of monocyte distribution width (MDW), which reflects the extent of monocyte differentiation into macrophages and dendritic cells in response to injury or infection. Children with severe COVID-19 had higher MDWs (>23) than healthy controls, and children with MIS-C had the highest MDW (mean: 32 ± 7.2). The authors emphasized that MDW values overlap across the spectrum of SARS-CoV-2 related illness and should only be used as a biomarker in combination with clinical presentation. Adding to these findings, Erdele et al[39] reported finding a statistically significant association between the mean platelet volume and cardiac involvement. Collectively, these data suggest hematological indices can provide important diagnostic and prognostic information.

Upregulation of Phospholipase A2 Group IIA (PLA2G2A)

In addition to the cell-mediated processes discussed, phospholipase A2 group IIA (PL–2G2A) is a protein which is believed to contribute to MIS-C pathophysiology. It will be briefly highlighted here as it pertains to thromboembolism risk, which is increased in MIS-C. PLA2G2A is a secreted protein which functions in phospholipid metabolism in bio-membranes and may cause vessel injury through the hydrolysis of cell membranes. It is increased in the circulation of patients with severe sepsis as well as in adult COVID-19 patients who died of COVID-19 disease, compared to survivors or patients with mild disease.[40] In a study of 50 patients with SARS-CoV-2 infection and 26 healthy control patients admitted to a US hospital, Diorio et al[41] found that protein signatures demonstrate overlap between MIS-C, macrophage activation syndrome (MAS) and thrombotic microangiopathy (TMA), which are all inflammatory syndromes, and that PLA2G2A is a marker of MIS-C with features of TMA.[42,43]

Direct SARS-CoV-2 Viral Invasion

Direct SARS-CoV-2 viral invasion provides an additional mechanism of injury in severe MIS-C. In a study from Sao Paulo, Brazil, Duarte-Neto et al[44] reported on findings from post-mortem studies of five children and adolescents who died of illness associated with SARS-CoV-2. SARS-CoV-2 was detected in the heart, lungs, and kidneys of all five patients, in the brain of one patient, in the intestinal tissue of one patient, and in cardiac and brain endothelial cells of two patients with MIS-C.

Endothelial Cell Activation and Vascular Dysfunction

Endothelial cell activation and vascular dysfunction are key features of MIS-C. Degradation products of the endothelium have been found in the blood and urine of patients hospitalized with MIS-C.[45] Moore et al[45] analyzed blood and urine samples from 17 children with MIS-C and found elevated levels of breakdown products of the endothelial glycocalyx, the matrix that covers the apical side of vascular endothelium. Since the glycocalyx is involved in multiple vascular activities, including regulation of permeability, cytokine signaling, and thrombosis, glycocalyx injury impacts vascular function significantly. Not surprisingly, the degree of glycocalyx shedding correlated with TNF-α concentration and with MIS-C severity. Similar findings have been reported with other endothelial breakdown products, including syndecan-1 in blood samples and chondroitin sulfate in urine samples. Porritt et al[46] report that antibodies from serum of patients with MIS-C can bind to activated human cardiac microvascular endothelial cells in culture, suggesting potential antibody/vascular interaction

which may affect endothelial function in MIS-C patients. Gelzo et al[47] examined serum levels of MCP-1, VEGF-A and pANCA and documented different temporal changes in these biomarkers of endothelial damage in 45 hospitalized MIS-C patients.

To characterize vascular dysfunction in MIS-C patients, Kreslova et al[48] utilized the reactive hyperemia index (RHI), a measure of the magnitude of limb reperfusion following a brief period of arterial occlusion, and an established technique for noninvasive assessment of peripheral microvascular function. Blunted reactive hyperemia is an indication of impaired microvascular function and a predictor of all-cause and cardiovascular morbidity and mortality in adults.[49] In this study from the Czech Republic, 27 pediatric patients with MIS-C and 23 healthy controls were evaluated 3 or more months after MIS-C treatment at 3 hospitals. Patients with MIS-C exhibited a significantly lower RHI than healthy controls ($n = 23$), reflecting a substantial level of endothelial dysfunction. Additionally, the study looked at the association between RHI and serum levels of cystatin C (Cys C), a potential biomarker of increased cardiovascular risk in adults.[50] The data revealed that serum Cys C levels were independently associated with a diminished RHI, suggesting that Cys C may be a marker of endothelial dysfunction in MIS-C, and that the combination of increased serum Cys C and diminished RHI may further aid in predicting the cardiovascular consequences of MIS-C.

Ciftel et al[51,52] used ultrasound to evaluate endothelial dysfunction and arterial stiffness in 38 patients with MIS-C and 38 healthy controls in Turkey. Ventricular parameters and ascending aorta diameter were obtained using echocardiography. Endothelial function was evaluated using flow-mediated dilation, assessed by measuring the brachial artery diameter. Compared to healthy controls, the MIS-C group had decreased flow-mediated dilation, aortic strain and aortic distensibility, with correlations to reduced ejection fraction (EF). This study provides evidence that pediatric patients with MIS-C exhibit physiologically measurable endothelial dysfunction and arterial stiffness, which had direct correlations with reductions in EF.

In the clinical setting, vascular dysfunction may be manifested as vasoplegia, a condition in which systemic vascular resistance is inappropriately low in the presence of normovolemia and normal or increased cardiac output. A critical consequence of vasoplegia is an inability to maintain adequate blood pressure for organ and tissue perfusion, resulting in vasodilatory shock and end organ injury. Although cardiac dysfunction is a major cause of shock in MIS-C, vasoplegia may be an additional or concomitant etiology of shock. In a single center case-cohort study in the US, Alali et al[53] described the hemodynamic profile of 14 patients with MIS-C who were admitted to the ICU between March 2020 and May 2021 and who required vasoactive support for treatment of shock. These patients had hyperdynamic cardiac index (CI) and low systemic vascular resistance (SVRi) in the first 24 h, a reflection of the different etiologies of shock in MIS-C and the need for careful titration of medications with ionotropic, vasoconstricting, or vasodilating properties.

Gastrointestinal Tract—a Potential Source of SARS-CoV-2 Viral Antigenemia

Yonker et al[54] (U.S.) proposed that gastrointestinal (GI) sources of SARS-CoV-2 viral antigenemia may propel the development of MIS-C. SARS-CoV-2 Spike protein has been detected in stool samples using polymerase chain reaction (PCR) at the time of patient presentation with MIS-C weeks after the initial infection. Nasopharyngeal swabs from most MIS-C patients test negative for SARS-CoV-2 by PCR, while anti-SARS-CoV-2 IgG are often elevated, suggesting prior exposure. Mayordomo-Colunga et al[55] reported the presence of SARS-CoV-2 Spike protein in the intestinal cells of a patient with MIS-C; a relevant finding as viral invasion is known to compromise the blood-intestinal barrier. The increased permeability may provide a portal for Spike protein from the GI tract to enter the circulation. Supporting this idea, Jarmarillo-Esparza et al reported in a retrospective observational study in Mexico of 248 patients with acute COVID-19, that pediatric patients with COVID-19 have an increased risk of developing MIS-C if they exhibit gastrointestinal symptoms.[56] Yonker et al found that the level of zonulin, a protein that regulates intestinal permeability, is increased in the blood stream of patients with MIS-C.[54] This increase suggests zonulin dysfunction, which is associated with decreased intestinal barrier function. To investigate the possibility of restoring intestinal epithelial integrity, Yonker et al[57] are conducting a clinical trial in which Larazotide, an inhibitor of zonulin release, is used as one of the therapies for pediatric COVID-19 or MIS-C patients with gastrointestinal symptoms.

END-Organ Dysfunction

MIS-C is associated with compromised function in multiple organs. The most well studied organ systems will be reviewed here.

Cardiac Dysfunction

Cardiac injury has been reported in 50–80% of children who required hospitalization for MIS-C.[58] Cardiac pathologies include myocarditis, ventricular dysfunction, cardiogenic shock, cardiac arrhythmias, coronary artery dilations and coronary aneurysms.[11] Proposed pathways involve direct myocyte injury after the SARS-CoV-2 virus enters the myocyte via the angiotensin-converting enzyme 2, or ACE2 "receptor".[59] This is consistent with the high level of ACE2 expression in the heart, including the pericardium, adipocytes, fibroblasts, myocytes, and coronary arteries.[60] Additionally, the hyperinflammatory state associated with COVID-19 infection also causes myocyte damage by T-lymphocyte activation and cytokine release.[59]

Reported cardiac manifestation varies, with data showing acute heart failure to be one of the most common cardiac presentations in MIS-C. Cardiac presentation includes left ventricular (LV) dysfunction (28-55% of patients), coronary artery dilation

or aneurysms (12%-21% of patients), myocarditis (17%-18% of patients), and pericardial effusion (23% of patients).[4] Jone et al[58] reported that 50% of MIS-C patients with cardiac abnormalities experience cardiogenic shock. Cardiac markers such as troponin and BNP are commonly elevated.[61] In a small cohort study, Kelly et al[62] observed that elevation of cardiac markers paralleled the severity of echocardiographic findings in children with MIS-C. Electrocardiographic changes are not specific and include sinus tachycardia, ST elevation, T wave changes, QRS prolongation, atrioventricular block, and bundle-branch block.[61] Cardiac echo typically shows regional or global hypokinesia and myocardial edema,[59] and may include left ventricular dysfunction, valvulitis, coronary artery changes, and pericardial effusion.[63] Cardiac MRI is also used to diagnose myocarditis based on the Lake Louise Consensus Criteria, which includes myocardial edema and another marker of inflammatory myocardial injury such as: 1) global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted images and 2) increased myocardial T1, extracellular volume, or late gadolinium enhancement.[64] Limited data from post-mortem examinations in pediatric patients with MIS-C showed cardiac interstitial and perivascular myeloid inflammation without necrosis and prominent epicardial and peri-vascular inflammation without vessel involvement.[65] COVID mRNA has been recovered in some cases.[59] Dolhnikoff et al[66] reported the presence of SARS-CoV-2 antigen in cardiomyocytes and cardiac endothelium, along with diffuse perivascular interstitial inflammation, severe myocarditis, and cardiac necrosis. De Cervins et al[67] reported that MIS-C patients with myocarditis had sustained nuclear factor kappa-B (NF-κB) activity and TNF-α signaling, as well as decreased type I and type II interferon responses in their monocytes and dendritic cells, compared to MIS-C patients without cardiac involvement. These data highlight the active role of monocytes and dendritic cells in the pathophysiology of myocarditis in MIS-C.

Alsaied et al[11] described the characteristics of coronary artery dilation and aneurysms s in MIS-C,[10,68,69] with coronary abnormalities reported in 6% to 24% of patients.[70,71] Although the majority of patients demonstrated small aneurysms, there have been rare cases of large/giant aneurysms (z-score ≥ 10) and aneurysms that developed later during the convalescent period.[1,68] The pathologic mechanism of coronary artery dilation and aneurysm is postulated to be related to fever and circulating inflammatory mediators, with disruption of the arterial wall as is seen in KD. Most patients are started on antiplatelet therapy, and most cases are mild and do not result in thrombosis or ischemia.

Cardiac-specific treatment include supportive therapy for cardiogenic shock, using standard ionotropic agents including epinephrine, norepinephrine, and dopamine, anti-arrhythmic medications as needed, and IVIG as an immune-modulating agent. Many of the abnormalities have resolved by the time of short-term follow-up. Most patients with LV dysfunction had resolution at 6 months, and even the few with persistent abnormalities had very mild dysfunction that was no longer clinically significant during follow-up.[58] Outcomes with regard to coronary artery dilation and aneurysms in MIS-C have been favorable with many abnormalities normalizing within 30 days,[72] although 5.2% of patients had persistent abnormities at 6 months follow-up.[73] Long-term outcomes are not yet known, but short-term outcomes are better than that in KD, which may rarely include thrombosis or aneurysm rupture.[74] The current recommendation is to repeat an echo 4–6 weeks after diagnosis to screen for late aneurysms.[11]

Pulmonary Dysfunction

Severe pulmonary disease is less prevalent in MIS-C compared to acute COVID-19. Lung pathology could result from the hyper-inflammation or secondary to cardiac pathology. Respiratory failure resulting in the need for invasive mechanical ventilation (MV) has been reported in 30%-70% of pediatric COVID-19 patients and 15–18% for patients with MIS-C.[10,75] Ghezzi et al[63] reviewed lung imaging of 21 patients with a diagnosis of MIS-C admitted to a hospital in Italy between October 2020 and February 2021. Chest X-ray (CXR) and lung ultrasound (U/S) were performed within 24–48 h of admission. Pulmonary abnormalities were found in all patients by CXR, with perihilar interstitial thickening being the most common finding. Other abnormalities included consolidations in the lower lobes and pleural effusions. 18 patients had abnormal findings on ultrasound, including B lines in the lower lobes. Pulmonary function was assessed in every patient by structured light plethysmography (SLP). A mild obstructive disorder was observed in 15/21 patients (71.4%). Six months after hospital discharge, all patients had normal findings on echocardiography, lung US, SLP and spirometry. In another study, Ibrahim et al[76] reviewed all critically ill patients ($n = 35$) with MIS-C admitted to the a pediatric intensive care unit in Egypt from June to July 2020, when the syndrome was a novel diagnosis and pulmonary CT was performed for all severe MIS-C patients within 48 h of admission. Although most patients did not have respiratory manifestations, 22 (71%) had pulmonary CT findings, including architecture distortion, consolidation ground glass opacities pleural effusion and/or thickening, and axillary and mediastinal lymphadenopathy. In a retrospective study, Biko et al[77] analyzed lung imaging in pediatric patients with COVID-19 and MIS-C from March to May 2020. During this period, 313 (5%) tested positive for SARS-CoV-2 associated parameters. Of these, 92/313 (29%) were asymptomatic and 55/313 (18%) were admitted to the hospital. US, CT, or MRI was performed in 23 out of 55 children, 9 of whom had MIS-C. CXRs were the most common examination (51/55 s), and chest CT was the least common (1/55) and most demonstrated no abnormality (34/51). The most common acute finding was interstitial opacities (in 8 of 10 children with MIS-C), alveolar opacities (2/10), followed by pleural effusion (4/10).

Dominguez-Rojas et al[78] conducted an observational study of pediatric patients with acute COVID-19 or MIS-C who required mechanical ventilation in four pediatric referral

hospitals in Peru. They found that lung mechanic parameters differed between the groups, with a higher elastic component in patients with acute COVID-19 and a higher resistive component in patients with MIS-C. The use of pressors was more frequent in the MIS-C group, even after excluding patients with moderate and severe left ventricular failure to exclude cardiogenic pulmonary edema. Both groups had similar LOS in the PICU, but intubated pediatric patients with acute COVID-19 had fewer ventilator-free days and higher mortality. The patients with COVID-19 had higher driving pressure, with lung mechanics similar to that in classic ARDS, while the patients with MIS-C had a wider difference between plateau and peak pressure, with lung mechanics similar to that in obstructive pulmonary failure.

Gastrointestinal Dysfunction

Gastrointestinal disturbances are common in MIS-C, with symptoms in up to 60–85% of cases.[54,72,79–85] Common symptoms include abdominal pain, nausea, vomiting, and diarrhea, and are usually mild and transient, although more severe or prolonged symptoms have been reported. Miller et al[86] reviewed data of 44 patients with MIS-C (single hospital, U.S., April—May 2020) and found that most patients had markedly elevated inflammatory markers, including ESR, CRP, and mildly decreased albumin. Transaminases were elevated in 52.3%, and lipase was elevated more than 3 times the upper limit of normal in 1 patient. Imaging studies were obtained in 15 patients. 3 patients (20.0%) had normal findings; others had findings of mesenteric adenitis, biliary sludge or acalculous cholecystitis, ascites, mesenteric fat edema, and bowel wall thickening. In a report of 8 patients with MIS-C and 4 patients with acute COVID-19 at 2 hospitals in Italy, Amoroso et al[87] found that vascular thrombosis was a major cause of the presentation of acute abdomen.

Sayed et al[82] performed a retrospective review of the Viral Infection and Respiratory Illness Universal Study registry, in a prospective observational, multicenter international cohort study of hospitalized children with acute COVID-19 or MIS-C from March to November 2020. In a cohort of 789 patients, GI involvement was present in 500 (63%). Critical illness occurred in 392 (49%) patients and 18 (2.3%) patients died. Those with GI involvement were older (median age of 8 yr), and 18.2% had an underlying GI comorbidity. GI symptoms and liver derangements were more common among patients with MIS-C.

Chen et al[88] cited findings from a literature review, reporting that 90% of 72 children with MIS-C had gastrointestinal manifestations, mostly abdominal pain, vomiting, and diarrhea, and that 10% of these patients had rare presentations mimicking appendicitis and peritonitis. In a multicenter retrospective cohort study of 695 children in Italy, of whom 91.7% had acute COVID-19 and 8.3% had a diagnosis of MIS-C, Lo Vecchio et al[89] reported that the presence of GI symptoms was associated with a higher risk of hospital and ICU admission. Sixty-five children (9.5%) showed severe GI involvement, including disseminated adenomesenteritis (39.6%), appendicitis (33.5%), abdominal fluid collection (21.3%), pancreatitis (6.9%), or intussusception (4.6%). In a single center retrospective review from Turkey, Boybeyi-Turer et al[90] also reported a high prevalence of abdominal symptoms in a cohort of 13 children with MIS-C and 2 with COVID-19, and the symptoms often overlap with those of appendicitis, intussusception, and inflammatory bowel disease. Amoroso et al[87] performed a retrospective case control study to evaluate the histological characteristics of SARS-CoV-2 positive pediatric patients undergoing laparoscopic exploration for acute abdomen. The study enrolled 8 MIS-C patients and 4 SARS-CoV-2 positive patients who underwent intestinal resection versus 36 control appendectomies from 2 pediatric tertiary referral centers in Italy between March 2020 and July 2021. All SARS-CoV-2 related surgical samples showed thrombotic patterns, which were significantly less frequent in SARS-CoV-2 negative appendectomies, suggesting that SARS-CoV-2 can cause thrombotic damage in abdominal tissues both in acute COVID-19 and in MIS-C.

Neurological Dysfunction

COVID-19 infection in children, as in adults, has been associated with a range of central and peripheral neurologic complications, including encephalitis, meningitis, acute demyelinating encephalomyelitis (ADEM), posterior reversible encephalopathy (PRES), cerebral vasculitis, cerebral venous sinus thrombosis (CVST), development of cytotoxic lesions and acute cerebral edema, acute hemorrhagic necrotizing encephalitis, Guillain Barre Syndrome (GBS), transverse myelitis, and cerebellitis.[91,92] The mechanisms underlying these various pathologies may include direct viral infection of CNS from hematogenous or retrograde dissemination, neuroinflammation, post-infectious immune dysregulation, or secondary injury from a hyperinflammatory state. Patients with MIS-C frequently have neurologic symptoms, and pediatric case series have found a high incidence of neurologic involvement—in 12–47% of patients in patients meeting criteria for MIS-C.[69,93–98] In one large, multicenter registry of pediatric patients admitted to 5 hospitals in the U.S. with acute COVID-19 or MIS-C, LaRovere et al[97] reported that 35% of the patients with MIS-C had neurologic involvement. Overall,12% of patients in this report had "life-threatening neurologic conditions," including severe encephalopathy, ischemic or hemorrhagic stroke, GBS, acute CNS infection or ADEM, or acute fulminant cerebral edema. ADEM appeared to be the most common complication associated with MIS-C. followed by cerebrovascular disease. Patients with MIS-C and neurologic involvement may present with severe headache, altered mental status, behavior changes, hypersomnia, altered consciousness, weakness, seizures, meningismus, or cranial nerve palsies. In a retrospective study of 75 patients admitted to a hospital in England from March to June 2020, Sa et al reported that children with neurologic features of MIS-C had significantly higher inflammatory markers than children with MIS-C without neurologic features, lending support to the hypothesis that the neurologic involvement in MIS-C may be immune-mediated.[99]

MIS-C encephalitis remains poorly understood. SARS-CoV-2 in rare instances has been isolated from the CSF of patients with acute COVID,[100] and has also been identified in brain tissue on autopsy, even months after acute infection. However, encephalitis may arise from immune-mediated mechanisms secondary to cytokine storm, monocyte and macrophage activation and the release of inflammatory mediators such as interleukin-6 (IL-6).[101,102] Hypothesized mechanisms include endothelial injury, inflammation, and activation of inflammatory cascades.[103] Lesions of the corpus callosum have been reported on imaging, and may indicate signs of selective vulnerability, particularly of the splenium to cytokine storm, due to a high density of cytokine and glutamate receptors in this area.[104] Neurological dysfunction at 6- and 12-months after hospital discharge have been documented, raising concern regarding the persistence of neuropsychiatric abnormalities.[105]

Renal Dysfunction

Acute kidney injury (AKI) occurs in 25% to 33% of the patients with MIS-C.[106,107] The mechanism is believed to be multifactorial and described in a review by Sethi et al[108] as a combination of renal vascular injuries due to endothelial dysfunction and complement and coagulation activation,[109] imbalance in renin-angiotensin-aldosterone system activation promoting glomerular dysfunction and vasoconstriction,[110] obstruction of the glomerular capillaries by red blood cells similar to the case in thrombotic microangiopathy,[111] and drug toxicity and organ cross-talk effects.[111–113]

Tripathi et al[114] performed a systematic review and meta-analysis describing incidence, mortality, and need for renal replacement therapy (RRT) in patients with MIS-C; based on 24 multi-center studies, with 6186 children included in the systematic review and 11 of these studies with 4947 children included in the meta-analysis. The proportion of patients with MIS-C developing AKI was 20%, with 20–23% of these patients requiring renal replacement therapy (RRT), suggesting that patients with MIS-C have a similar risk of AKI and RRT requirement when compared to the general population of pediatric patients in the ICU (5-37%),[115,116] most commonly with the use of high flow continuous veno-venous hemodiafiltration.

AKI was associated with high ferritin levels, use of nephrotoxic drugs, need for vasoactive medication, and longer duration of ICU stay,[106,107] well as with elevations in sC5b9, a measurement of complement activation.[43] Viral infection of the cell, complement activation and vascular injury have also been proposed as etiologies.[43] Overall mortality in MIS-C patients in this study was 4%, with an increase in mortality by 4.68 times if the patients develop AKI, analogous to mortality among general PICU patients with and without AKI.[115,116]

Coagulation Dysfunction and Thrombo-Embolism

MIS-C is associated with increased rates of thrombo-embolism (TE).[117] There are multiple contributing factors—endothelial injury, platelet activation, alteration in coagulation factors, impaired fibrinolysis,[118] increased tissue factor,[119] neurotrophic extracellular trap formation,[19] dysregulated complement activation,[120] and decreased fibrinolysis.[121] Children with severe COVID-19 and MIS-C have been diagnosed with complement-mediated thrombotic microangiopathy (TMA), thrombocytopenia and microangiopathic hemolytic anemia,[122] along with vascular-endothelial dysfunction.[117] Indices of hypercoagulability have also been documented in patients with MIS-C using thromboelastography (TEG).[123,124]

Rajput et al and Feldstein et al investigated the extent of symptomatic VTE in patients with MIS-C, found to be 7% among patients 13–20 years of age.[69,125,126] Whitworth et al anaIyzed EHR data associated with 853 admissions to eight US hospitals from March to August 2020 (426 admissions for COVID-19, 138 for MIS-C, 8 for presumed MIS-C, 289 for asymptomatic SARS-CoV-2 infection),[127] and reported the incidence of thrombosis as follows—COVID-19 −2.1%; MIS-C—6.5%; asymptomatic SARS-CoV-2 infection-0.7%.[127] The mortality rate was 28% in pediatric patients with COVID-19 or MIS-C and thrombo-emboli (TEs); these patients often had comorbidities that were risk factors for TE, including cancer, hemothorax, renal failure, thrombotic microangiopathy, complex congenital heart disease, and bowel obstruction. In a single center in the U.S., Rajput et al[126] reported that 1 out of 116 patients with MIS-C (March 2020-December 2021) developed symptomatic non-catheter related superficial vein thrombosis. Trapani et al[128] performed a systematic review of all relevant studies published in English from January 2020 through June 2022, including 62 studies with 138 patients who had TEs associated with SARS-CoV-2 infection or MIS-C. As expected, TEs were more commonly found in older children and adolescents, as well as in MIS-C who developed severe ventricular dysfunction or coronary artery aneurysms. Patients with pre-existing risk factors for thrombosis, and the need for a central venous line were more susceptible.[127–129] Venous thromboses were the most common (85 events, 54%), including deep vein thrombosis, central cerebral venous sinus thrombosis, pulmonary embolism, and splanchnic vein thrombosis. Arterial thrombosis (38 events, 59%) have been found in cerebral arteries, coronary arteries, and systemic peripheral arteries, and may cause acute significant pathology, including ischemic stroke, intracardiac thrombosis, limb ischemia, and multiple organ failure. 61% of the patients had at least one condition that pre-disposed to TE, most commonly cancer and obesity. 17 of the 138 patients with TE died (mortality rate 12%); most of them had arterial thrombosis. Most patients completely recovered or were improved at discharge or at follow-up; 6% had persistent sequelae of acute ischemic stroke.

Based on consensus opinions of experts from the Pediatric/Neonatal Scientific and Standardization Subcommittee of the International Society of Thrombosis and Haemostasis, Goldenberg et al[130] proposed a regimen for thromboprophylaxis for children with MIS-C and additional risk factors for VTE, consisting of prophylactic-dose enoxaparin at a standard

starting dose and adjusted to achieve a target anti-factor Xa range of 0.1–0.3 U/mL, a goal which was shown to be achievable in a study with 38 pediatric COVID-19 patients.[126] In a single-center retrospective cohort study of children treated according to this guideline, there were no cases of significant DVT in 116 of 121 patients with confirmed MIS-C when target Xa level was achieved in 24 h of admission. This regimen appears safe, with reports of a small number of bleeding events in patients with co-morbidities. Whitworth et al[127] reported that 9 patients (1.5%) had major bleeding and 8 (1.4%) had clinically non-major bleeding, out of a total of 436 patients with COVID-19 and 138 patients with MIS-C who received prophylactic anticoagulation. Rajput et al[126] found that 5 patients (4.3%) had clinically relevant nonmajor bleeding. To balance each patient's clotting versus bleeding risk, Sharathkumar et al[131] proposed an algorithm for a personalized assessment of thromboembolism and bleeding risk, incorporating each patient's baseline risk factors for TE and for coagulopathy, along with severity of infection or MIS-C, age, genetics, and markers of inflammation, in the decision regarding intensity of anticoagulation (prophylactic vs therapeutic), choice of anticoagulant, duration of therapy, and outcome measures.

Treatment and Therapies

When MIS-C initially surfaced as a disease entity, the treatment was variable, primarily derived from institutional expert consensus opinion. By building on clinical experience, treatment strategies have evolved along several standard modalities. Feldstein et al[69] analyzed surveillance data from March to May 2020, synthesizing characteristics of 186 patients with MIS-C in the U.S. Of this cohort, 148 (80%) were required ICU care, 37 (20%) required mechanical ventilation, 90 (48%) received vasoactive therapies, 8 (4%) required ECMO and 3 (2%) died. 74 (40%) patients had KD-like features. 144 (77%) patients received IVIG, 91 (49%) received glucocorticoids, and 38 (20%) received interleukin-6 inhibitors (tocilizumab or siltuximab) or interleukin-1Ra inhibitor (anakinra). Tiwari et al[132] identified 41 patients meeting CDC case definition of MIS-C from two tertiary care centers in Kerala, India. 33 (80%) of patients were previously healthy and 8 (20%) had coexisting comorbidities including obesity, asthma, neurological disorders, or surgically corrected congenital heart disease. 23 (56%) of patients had abnormal echocardiogram findings including coronary artery aneurysms, left ventricular dysfunction, pericardial effusion or global/septal hypokinesia. Treatment was variable, with 39 (95%) receiving immunomodulatory therapy, 35 (85%) receiving steroids and IVIG, and in 3 (7%) receiving only steroids. 36 (88%) patients had severe illness and required ICU admission. 21 (51%) received inotropic support and 8 (20%) required mechanical ventilation. Many similar surveys have been done, with the majority reporting IVIG or dexamethasone as first-line agent, and the addition of glucocorticoids or IVIG if further therapy was required. Therapies that target pro-inflammatory cytokines might be added.

Glucocorticoids and Intravenous Immunoglobulin (IVIG)

Glucocorticoids are powerful immunomodulators that lead to inhibition of proinflammatory genes and have non-genomic effects on both immune and endothelial cells, further reducing inflammation. IVIG is theorized to modulate neutrophil activity and inhibit interleukin-1-β and subsets of T cell and endothelial cell activities. Additionally, IVIG may inhibit autoantibody production or directly neutralize autoantibodies in MIS-C.[133] These two therapies are often used in combination.

Welzel et al[134] conducted a randomized trial in a multicenter study in Switzerland, which compared methylprednisolone 10 mg/kg per day for 3 days (n = 37) to a single dose of IVIG 2 gm/kg (n = 38). There was no difference for the primary outcome of hospital LOS (6 days) or death (none). In a secondary analysis, 27% of patients in the glucocorticoid group required respiratory support compared to 55% of those in the IVIG arm, a statistically significant result.[23] There was no difference between the arms for the occurrence of coronary artery enlargement. The small sample size in this study limited the power for treatment comparisons, and many patients received additional therapies for MIS-C after randomization.

Targeting pro-Inflammatory Cytokines: Receptor Antagonists and Monoclonal Antibodies

Anakinra, an IL-1 receptor antagonist, has been used in the treatment of refractory KD and has shown efficacy in decreasing the rate of coronary artery aneurysm development.[135] Since IL-1α and IL-1β levels are also elevated in MIS-C, it is postulated that Anakinra might be similarly efficacious in the treatment of MIS-C. Similarly, the use of monoclonal antibodies that target cytokines is also modeled after their use in KD, since TNF-α and IL-6 are elevated in both MIS-C and KD[18,19,136] In this regard, the use of an anti-TNF-α antibody (Infliximab) and an anti-IL-6 antibody (tocilizumab) have been added to the list of potential therapies for MIS-C.

Combination Therapies and Treatment Strategies

During the early phase of the pandemic, there was significant variability among practice styles, as reported by Rosu et al[137] in a survey of 174 providers. The need for comprehensive and evidence-based guidelines for the treatment of MIS-C was soon recognized.[138,139] The Best Available Treatment Study (BATS)[140] involved a global effort to analyze the effects of different treatments on patient outcome, in which clinicians uploaded clinical information from patients with suspected or proven MIS-C into a Web-based Research Electronic Data Capture database. The study population included 614 children from 32 countries (June 2020 to February 2021). 124 of these patients did not meet WHO criteria for MIS-C, most often due to missing concrete evidence of SARS-CoV-2 exposure. Three primary treatments were evaluated: IVIG alone, glucocorticoids alone, and IVIG plus glucocorticoids. The primary outcomes were 1). need for inotropic

support or mechanical ventilation by day 2 or later, or death, and 2). reduction in disease severity between day 0 and day 2. Of the 614 patients, MIS-C, 246 were treated with IVIG alone, 99 with glucocorticoids alone, and 208 with IVIG plus glucocorticoids. 22 children were treated with other therapies, and 39 patients did not receive any immunomodulatory therapy. The time to reduction in disease severity was similar among the three groups, with no significant difference in the primary outcomes. However, a subgroup analysis that included only patients who met WHO criteria for MIS-C suggested a benefit of glucocorticoids alone over IVIG alone for reducing organ failure and disease severity. Notably, this comparison may have been influenced by the large percentage of patients with treatment escalation to IVIG plus glucocorticoids, thereby decreasing the number of patients receiving IVIG or steroids alone. Additionally, the group which received IVIG plus glucocorticoids tended to have more severe illness, which might have prompted therapy escalation. Secondary outcomes, such as time to reduction in organ failure and inflammation, were positive with all 3 therapies with no significant difference. The retrospective nature of this study precluded patient randomization for more directed comparisons, and the limitations encountered by the clinicians and researchers highlight the many challenges in performing this research. In another comparative study, Ouldali et al[141] retrospectively analyzed data from a national surveillance system in France from April 2020 to January 2021, including 181 children with suspected or diagnosed MIS-C. The data suggested that there was a higher failure rate with the use of IVIG alone compared to IVIG plus methylprednisolone. Son et al[81] conducted a retrospective propensity score matched analysis among 518 children hospitalized with MIS-C between March and October 2020, comparing the use of IVIG versus IVIG and glucocorticoids as initial therapy. Results suggested that initial treatment with IVIG plus glucocorticoids was associated with a lower risk of cardiovascular dysfunction after day 2 compared with IVIG alone. This study lends support to the combination approach. Shah et al[142] surveyed medications used in a cohort of 233 patients at 4 children's hospitals in the U.S. from March 2020 to March 2021. The most common therapies were steroids (88.4%), aspirin (81.1%), IVIG (77.7%) and anticoagulants (71.2%). Controlling for confounding variables, patients receiving IVIG within 1 day of hospitalization were less likely to have hospital length of stay ≥8 days. Patients receiving low-dose steroids within 1 day of hospitalization were less likely to develop ventricular dysfunction, increasingly elevated troponin levels, or hospital length of stay ≥8 days. Keeping in mind the retrospective nature of the study, these data supported the efficacy of IVIG and steroids in mitigating the more severe effects of MIS-C. Many additional studies on this subject have been performed and are listed a review by Sharma et al.[15]

Cole et al[143] compared the use of IVIG plus infliximab versus IVIG alone in a retrospective cohort study including 72 children with MIS-C who were hospitalized between April 2020 and February 2021 in a single U.S. center. MIS-C therapies started within 24 h of treatment initiation were considered as initial therapy. Patients were excluded if the initial therapy included treatments other than IVIG and/or infliximab. At the time, the MIS-C guidelines at the institution recommended IVIG alone as initial therapy, unless there was dilation of the right coronary artery and/or left anterior descending artery (z scores ≥2.5). These guidelines were later adjusted to recommend initial therapy with IVIG plus infliximab for any patients with right coronary artery and/or left anterior descending artery dilation (z scores ≥2.0), left ventricular dysfunction with ejection fraction <55%, and/or hypotension. In this study, the 72 eligible patients were subdivided into two groups: IVIG alone (20 patients) and IVIG plus infliximab (52 patients). The two groups were statistically similar, with no significant differences in age, race and ethnicity, underlying conditions, organ system involvement, and need for respiratory support or vasoactive medications. However, there were statistically significant differences in admission location, fulfillment of incomplete KD criteria, and presence of abnormal echocardiogram findings. -10% of the patients in the IVIG group were admitted to the ICU, compared to 56% of those treated with both IVIG and infliximab. 15% of the patients in the IVIG group met incomplete KD criteria compared to 42% in the dual treatment group. Coronary artery dilation and/or LV dysfunction was more common in the IVIG plus infliximab group (71%) compared with IVIG alone (40%). Primary outcome of this study was the need for additional immunomodulating agents, with data showing that IVIG plus infliximab was associated with a decreased need for additional therapies and decreased development of new or worsened LV dysfunction (8% in IVIG plus infliximab group compared with 25% in IVIG group), shorter median ICU LOS (3.7 compared with 4.5 days) and more rapid decrease in CRP. As the authors noted, propensity score matching was not performed due to the small sample size and the lack of statistically significant differences between the two groups, and the results may have been influenced by the increased severity of illness in the IVIG plus infliximab group.

Although IVIG is a commonly used immunomodulatory agent in the treatment of MIS-C, some institutional protocols do not recommend it as an initial agent due to concern that the large fluid volume of the infusion might worsen cardiac and pulmonary function. Licciardi et al[144] analyzed the outcomes of patients treated according to their institutional protocol in 2020, which utilized IV methylprednisolone alone as initial therapy, with addition of Anakinra as step-up therapy. IVIG was reserved for patients with suspected coronary artery aneurysm or persistent symptoms, or as a third line agent if needed. Of the 31 patients in this study, as initial therapy 25 received high dose pulse methylprednisolone (10 mg/kg) due to myocardial involvement and 6 received low dose methylprednisolone (2 mg/kg). Demographics were similar between the two groups, but pro-BNP level and the presence of hypotension were statistically different. 67.7% of the 31 patients responded to initial treatment with IV methylprednisolone. All patients recovered, with eight patients in the high dose methylprednisolone group receiving step-up therapy with Anakinra (25.8%) due to either persistent fever or CRP

increase. 2 of the 31 patients (6.5%) received an increased dose of methylprednisolone due to persistent fever. Four patients received IVIG—due to persistent irritability in one patient, suspected coronary artery dilation in two patients, and a small right coronary artery aneurysm in one patient. Overall, results suggest that an IVIG sparing protocol is a viable strategy that can lead to favorable outcomes in the treatment of MIS-C.

Jonat et al[145] discussed an institutional protocol for the management of MIS-C in a children's hospital in New York City. This protocol involved stepwise escalation of therapy based on the risk stratification of patients into mild, moderate, or severe categories. Patients who presented with low-level symptoms and who were considered by the clinician to have small risk of progressing to a significant hyperinflammatory state were not started on therapy on initial evaluation. Patients who met KD or incomplete KD criteria received IVIG, even if treatment for MIS-C were withheld due to low disease acuity at presentation. Further treatment was provided based on classification, which was determined by the Vasoactive-Inotrope Score (VIS),[7] amount of respiratory support, and evidence of organ injury. Mild cases—those with minimal signs of organ injury, requiring a low level of respiratory support, and no vasoactive medications—were treated with methylprednisolone 2 mg/kg/day, and additional pulse steroids or anakinra if illness was refractory. Moderate cases -those with VIS less than or equal to 10, significant supplemental oxygen requirement, and mild organ injury—were treated with methylprednisolone 10 mg/kg once followed by 2 mg/kg/day, additional pulse steroids if needed; then anakinra if refractory to pulse steroids. Severe cases—those with VIS greater than or equal to 10, need for ventilatory support, moderate/severe ventricular dysfunction or other significant organ injury- were treated with methylprednisolone 20–30 mg/kg/day for 1-3 days followed by 2 mg/kg/day. Anakinra was added in refractory cases, followed by tocilizumab if further escalation of therapy were necessary. All patients who were treated were administered broad-spectrum antibiotics until bacterial infection was excluded, as well as low molecular weight heparin prophylaxis or low dose aspirin, and IVIG 2 g/kg up to 100 g with a second dose in refractory cases. In total 54 patients were included, with 26 patients admitted before and 28 patients after protocol activation. None of these patients had severe presentations—none required invasive mechanical ventilation or mechanical circulatory support. Among the 54 patients who were hospitalized from March to June 2020, a total of 31 patients (57%) were admitted to the PICU. The authors noted that there were fewer PICU admissions after the protocol was implemented. Most of the patients (50/54), both pre and post protocol, received some form of immunomodulator, either glucocorticoid or IVIG. The lack of patients in the severe category, as well as the fact that the two groups were hospitalized at different time points in the epidemic, were limiting factors in the interpretation of the data, again illustrating the difficulties in performing comparative studies during a pandemic involving a new disease entity.

A single-center observational cohort study by Dizon et al,[146] conducted from May to November 2020, evaluated the use of Anakinra. Of 46 patients with confirmed MIS-C, 14 received IVIG, 23 received IVIG plus anakinra, and 9 received IVIG, corticosteroids, and Anakinra. A greater proportion of patients had presentation of shock in the IVIG plus Anakinra group—65% versus 21% in the IVIG monotherapy group. Patients with shock received a longer course and higher doses of Anakinra than those without. Patients treated with IVIG plus anakinra showed improvement in fever and cardiac function with or without corticosteroids. Overall, this study showed promising evidence for anakinra as an adjunctive therapy for patients with severe MIS-C.

A subsequent study by Jonat et al[133] investigated the impact of early treatment with glucocorticoids (within 48 h of admission) on hospital LOS. This multicenter retrospective cohort study took place between March to April 2021 and included 131 patients. The primary outcome was hospital LOS; secondary outcomes included ICU LOS, changes in pediatric sequential organ failure assessment (pSOFA) score, COVID-19 severity score, and duration of vasoactive or inotropic infusions. Early glucocorticoid treatment was associated with reduced pSOFA scores (2 vs1), improved COVID-19 severity scores (31% vs 11%) and shorter ICU LOS (4 vs9 days). It was noted that patients who received early glucocorticoids generally had lower mean arterial pressure within 24 h of arrival (54 mm Hg vs 62 mm Hg, comparing within similar age groups) and a higher rate of requiring vasoactive support (49% vs 17%), respiratory support, and ICU admission (74% vs 31%), Poisson regression was used to analyze the association between early glucocorticoid treatment and hospital LOS, with an adjusted analysis for all variables with a p-value <.1 in the bivariate analysis. This analysis showed that both early glucocorticoid and early IVIG administration were independently linked to shorter hospital LOS.

Algarni et al[139] compared clinical practice guidelines from different organizations and societies for the management of MIS-C, including those from the American Academy of Pediatrics (AAP), the American College of Rheumatology (ACR), the Spectrum Health Helen DeVos Children's Hospital (HDVCH), Nature Research, and Children's Hospital of The King's Daughters (CHKD). Although there were some differences in recommendations for pharmacologic therapies, there was a high level of consensus on the use of anti-inflammatory therapies including IVIG and steroid therapy, and antiplatelet therapy with low-dose aspirin. The authors proposed the use of a unified guideline that combines common recommendations from these institutions.

Anti-Coagulation and Antiplatelet Therapies

Thromboprophylaxis for pediatric patients with MIS-C posed an initial challenge as many factors needed to be considered including the effect of disease severity and co-morbidities on the risk of bleeding and the risk of thromboembolism. With similarities in presentation to that of KD, anti-coagulation and anti-platelet regimens were extrapolated from the 2017 American Heart Association Guideline for management of Kawasaki Disease. This topic is further discussed in section *2.9*.

CDC Guidelines

To develop initial guidelines for the management of MIS-C, a panel of experts was convened by the CDC to evaluate evidence from available clinical studies. The experts formulated a set of recommendations, providing a rating for the strength of each recommendation and a rating for the evidence that supports the recommendation, as well as the rationale and dosing guidelines. (CDC guidelines are available at https://www.covid19treatmentguidelines.nih.gov/). For initial therapy for patients hospitalized with MIS-C, the guidelines recommend IVIG in combination with low to moderate doses of glucocorticoids. Glucocorticoid monotherapy as an alternative initial treatment is recommended only if IVIG is unavailable or contraindicated. Conversely, IVIG monotherapy is recommended only if glucocorticoids are contraindicated.

A positive response to immunomodulatory therapy is generally manifested as clinical improvements within 24 h of treatment, with resolution of fever, improvement of organ function, and reduction of levels of inflammatory markers, particularly CRP. Conversely, worsening trends usually signal refractory disease that requires escalation of therapy. For children with refractory MIS-C, the Panel recommends additional immunomodulatory therapy with high-dose anakinra, higher-dose glucocorticoids, or infliximab**.** In some patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids plus anakinra or higher-dose glucocorticoids plus infliximab**.** Anakinra and infliximab should not be used in combination. A second dose of IVIG is not recommended for intensification therapy for patients with refractory MIS-C. Infliximab should not be used in patients with MIS-C and features of macrophage activation syndrome. Patients who receive multiple immunomodulatory agents should be monitored closely due to increased risk of infection.

To mitigate the increased thromboembolism risk in MIS-C, CDC guidelines recommend the use of low-dose aspirin for patients who do not have risk factors for bleeding. Children treated with aspirin and steroids should receive prophylactic H2 blockers or proton pump inhibitors. Patients with MIS-C who have large CAAs (Z-score $\geq$10) should receive therapeutic anticoagulation according to the American Heart Association guidelines for Kawasaki disease. Patients with MIS-C and moderate to severe left ventricular dysfunction who have no risk factors for bleeding should also receive therapeutic anticoagulation**.**

Mechanical Support

Mechanical ventilation is the most common form of mechanical support in the treatment of patients with MIS-C. Mechanical ventilation for MIS-C patients include oxygen administered by routine face mask and nasal cannulas, high flow nasal cannulas, non-invasive positive pressure ventilation using BIPAP or CPAP, and invasive positive pressure ventilation through endotracheal intubation. Mechanical ventilation strategies align with those used in general PICU patients, depending on whether their physiology fall within the category of mild, moderate, or severe respiratory distress.

Extracorporeal life support (ECLS), most commonly using extracorporeal membrane oxygenation (ECMO), is a rarely used but important rescue therapy for a small number of patients with MIS-C. Bembea et al[147] published a comprehensive analysis of ECMO requirement in MIS-C or acute COVID-19. Of the 2733 eligible pediatric patients admitted to the ICU and meeting CDC definition for MIS-C or acute COVID-19, there were 1530 MIS-C patients and 1203 patients with COVID-19. 37 (2.4%) MIS-C patients, and 71 (5.9%) COVID-19 patients required ECMO. Lack of COVID vaccination was a common factor in both groups, although more of the patients with MIS-C were not eligible for vaccination. ECMO was generally initiated earlier (median 1 vs 5 days from hospital admission) for MIS-C compared to acute COVID-19. As expected, patients with MIS-C required veno-arterial ECMO more often for cardiac dysfunction, and patients with acute COVID-19 required veno-venous ECMO more often for respiratory failure. Extracorporeal cardiopulmonary resuscitation (ECPR) rates were comparable in the MIS-C (19%) and acute COVID-19 (13%) groups. High levels of ferritin and of inflammatory markers were seen in patients with MIS-C that required ECMO.[132,148,149] Recognizing that children with MIS-C may require specialized support, Naber et al highlighted the importance of timely and direct communication between referral centers and referring institutions, to allow for the safe and punctual allocation of ECMO when necessary.[150] Renal replacement therapy (RRT) is another form of support that is rarely needed but necessary in the patients with MIS-C who have developed severe AKI. The proportion of patients with MIS-C developing AKI has been reported to be approximately 20%, with 20–23% of these patients requiring renal replacement therapy (RRT).[114] These numbers are comparable to those in the general PICU population with comparable disease severity. Due to the frequency of hemodynamic instability, high flow continuous veno-venous hemodiafiltration is the most commonly used form of RRT in this group of patients.

Therapeutic plasma exchange (TPE) has been reported as a treatment modality in MIS-C by Emeksiz et al[151] in an observational, descriptive, retrospective study in a PICU in Turkey. Of 65 patients with MIS-C of different severities, 27 patients with severe MIS-C were treated with TPE as an initial therapy. Patients were scheduled to undergo TPE if they had early acute lung injury, hypotension despite inotropic support, progression to multiple organ failure, lung infiltrates >50% within 24–48 h, or LV ejection fraction (LVEF) < 50%. TPE was used upon admission and repeated as needed with a 24 h delay after administration of any therapeutic medications. The authors reported a reduction of PELOD scores after TPE, with the limitations of small sample size and the retrospective observational nature of the study.

Vaccines and MIS-C

Vaccination against SARS-CoV-2 has been shown to decrease the rate of acute COVID-19 infection and of MIS-C.[152–156] In the fall of 2021, Pfizer presented results of a prospective,

placebo-controlled, phase 3 trial of their mRNA vaccine in 5- to 11-year-old children in which about 1500 children received 2 doses of the vaccine given 3 weeks apart and 750 children received placebo. At least 1 week after the second dose, 16 cases of symptomatic COVID-19 occurred in the placebo group and 3 in the vaccine group for a calculated efficacy of 90.9%.[157] Subsequently, two other studies evaluated the efficacy of 2 doses of Pfizer's mRNA vaccine administered to children aged 5–11 years from November 2021 to March 2022.[158,159] The protective efficacy was 31% against asymptomatic or symptomatic infection, 46% against emergency department or urgent care, and 74% against hospitalization. In 2023, Watanabe et al reported on results of a systematic review and meta-analysis that included 17 published studies of 10,935,541 vaccinated and 2,635,251 unvaccinated children—providing data that mRNA vaccines protected children against serious acute disease caused by SARS-CoV-2.[160]

Vaccination against SARS-CoV-2 is also associated with a lower risk of MIS-C.[147–149] Zhang et al reported that 92.1% (1332/1446) of MIS-C cases occurred in unvaccinated children, whereas 3.7% (54/1446) occurred in partially vaccinated and 4.2% (60/1446) in fully vaccinated children.[154] Additionally, an analysis was done by Yousaf et al that included all individuals aged 5–20 years in the MIS-C national surveillance dataset. This study demonstrated that those who have completed the two-dose primary series of COVID-19 vaccination had less severe disease than their unvaccinated counterparts.[153] Unvaccinated MIS-C patients had a 23% higher risk of ICU-level care compared with vaccinated MIS-C patients, though there were no significant differences in hospital or ICU length of stay. Overall, studies such as these support the efficacy of COVID vaccination in decreasing MIS-C incidence and severity.

In regards to potential harm associated with COVID-19 vaccines, a very small number of patients have developed an MIS-C-like inflammatory illness after vaccination, with the most severe adverse effect being myocarditis and pericarditis.[161,162] This disease entity is commonly known as multisystem inflammatory disease after COVID-19 vaccination (MIS-V) and has been reported in studies from many parts of the world,[163–172] with a universally low incidence. In an analysis including 21,335,331 individuals aged 12–20 years who had received one or more doses of a COVID-19 vaccine in the U.S. as of August 31, 2021, 21 individuals with MIS-C were identified, making the overall reporting rate for MIS-C after vaccination 1.0 case per million individuals receiving one or more doses in this age group. All 21 individuals were hospitalized; 12 (57%) were admitted to an intensive care unit and all were discharged home. The median age was 16 years (range 12-20); 13 (62%) were male and eight (38%) were female. 15 (71%) had laboratory evidence of past or recent SARS-CoV-2 infection, and six (29%) did not. The reporting rate in only those without evidence of SARS-CoV-2 infection was 0.3 cases per million vaccinated individuals.

Another analysis[164] of the myocarditis risk was done by Patone et al in a group of greater than 40 million people aged 13 and over who received at least 1 dose of ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer), or mRNA-1273 (Moderna) vaccine and were admitted to the hospital or died from myocarditis between December 2020 and December 2021.The results were stratified by age and sex. The risk of vaccine-associated myocarditis was found to be small, with up to an additional 2 events per million people in the 28-day period after exposure to all vaccine doses other than mRNA-1273. This is a substantially lower number than the 35 additional myocarditis events observed with SARS-CoV-2 infection before vaccination. However, when age and sex are taken into account, the risk of vaccine-associated myocarditis is consistently higher in younger men, particularly after a second dose of mRNA-1273; the number of additional events during those 28 days was estimated to be 97 per million people exposed. An important finding is that the risk of myocarditis in this group during the study time period was higher after a second dose of mRNA-1273 than the risk after infection. In younger women, the number of additional events per million after a second dose of mRNA-1273 was similar to the number after infection. Reassuringly, left ventricular longitudinal strain (LVLS) was reported by Nv et al[173] to be mild in the majority of patients at presentation and improved during convalescence. On the other hand, a retrospective observational multicenter study conducted by Jain et al from April 2021 to November 2022[163] showed that patients with COVID-19 vaccine-associated myocarditis (termed C-VAM by the authors) had a higher prevalence of myocardial scarring (manifested as late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging) at follow-up at a median of 178 days. Despite presenting with a lower degree of cardiac dysfunction than patients with MIS-C, patients with MIS-V had higher troponin levels and a higher prevalence of LGE during the acute illness as well as at follow-up exam. One proposed explanation for this discrepancy is that cardiac dysfunction in C-VAM results from direct myocardial injury, whereas in MIS-C it is a downstream effect of overall systemic inflammation, and distinct inflammatory and androgenic states have been identified in the two groups.[163,174] The persistence of LGE, a marker of myocardial scarring, warrants close monitoring of these patients to determine any long term functional effects.[163] In an ongoing study, the vaccine-associated myocarditis/pericarditis (CAMP) study, Truong et al will collect hospital and follow-up data for up to 5 years after illness onset.[175] Another study suggested that increasing the time interval between booster doses may decrease the risk of MIS-V.[169] Research endeavors such as these will provide guidance regarding the optimal type and timing of vaccines offered to children and adolescents acknowledging the risk -benefit profile of the individual and the prevalent COVID strain(s) in circulation as the landscape of SARS-CoV2 phylogeny continues to evolve.[164,176]

The question has been raised as to whether administration of COVID-19 vaccines is safe for children with a history of MIS-C. An international study found no relapses or additional severe inflammatory side effects following administration of COVID-19 vaccines to 273 patients with a history of MIS-C.[72] Of note, the data was collected in 32 countries with

substantial variations in vaccine policies—while universal vaccination is recommended in some countries for children over 6 months old, vaccination is recommended in other countries for children only if they have a chronic health condition that increases the risk of severe SARS-CoV2 disease. In spite of this limitation, it appears that COVID-19 vaccination does not cause additional adverse effects when administered to children with a history of MIS-C, compared with children without a history of MIS-C.[72,177]

Multisystem Inflammatory Syndrome in Neonates (MIS-N)

Multisystem Inflammatory Syndrome has been reported in the neonatal population (MIS-N) and is also characterized by elevated inflammatory markers and the detection of serum antibodies against the SARS-CoV-2 virus. The prevalence of SARS-CoV-2 infection in neonates born to a mother with viral positivity during pregnancy is estimated to be ~2% and of those infants that test positive, 50% are symptomatic.[178] Similar to other patient cohorts, SARS-CoV-2 symptomatology in neonates is heterogenous and varies in severity.[179] MIS-N diagnosed within the first three days of life is referred to as early-onset and between three and 28 days of life is considered late-onset. Though MIS-N is uncommon, the mortality rate has been reported as 8–10%.[180,181]

Pathophysiology of MIS-N

The pathophysiology of MIS-N remains poorly understood, in part due to the conflicting mechanistic theories regarding vertical SARS-CoV-2 transmission. As previously described, the ACE2 receptor in conjunction with the serine protease TMPRSS2 enables the SARS-CoV-2 virus to infect cells in multiple organs.[182] One case study conducted found that the placenta of infected mothers rarely (2 of 19) had evidence of SARS-COV-2 virus.[183] The authors concluded that the rarity of infected placental tissue may be at least in part due to the limited expression of TMPRSS2 and the preferential expression of ACE2 receptors away from the maternal vasculature.[183] The available evidence is most congruent with maternal SARS-CoV-2 infection and transfer of maternal antibodies to the fetus which leads to a complex immunological cascade of events including aberrant inflammation.[184,185] Alternative theories have speculated that MIS-N is the result of cervicovaginal transmission of the virus during the second stage of labor or due to infection acquired during the early postnatal period.[179,182,184,185]

Clinical Manifestations of MIS-N

Clinical manifestations of MIS-N range from mild to severe and include: rash, thermoregulatory changes, feeding problems, respiratory distress, seizures, coagulopathies, persistent pulmonary hypertension, myocarditis, cardiac ventricular dysfunction, and arrhythmias.[179,182,186] In early 2023, Mascarenhas et al published a review of 27 studies that included a total of 104 patients diagnosed with MIS-N. 84% of patients presented with cardiac pathology, 64% presented with respiratory symptoms, and 20% presented with fever.[182] General diagnostic criteria include manifestation of symptoms within the first 28 days of life, the involvement of two or more organ systems, elevated inflammatory biomarkers (particularly IL-6 and D-dimer), evidence of SARS-CoV-2 antibodies or a maternal history of infection or exposure during the peripartum period, and the absence of an alternative diagnosis.[181,182]

Treatment of MIS-N

Treatment for MIS-N centers on supporting the infant's hemodynamics with mechanical ventilation, inotrope therapy, and careful fluid balance as well as the administration of systemic steroids and IVIG. Medical providers caring for ill neonates must maintain a high index of suspicion for this heterogeneous syndrome. Future work should be aimed at understanding the pathophysiologic mechanisms to improve diagnosis and inform targeted therapy.

Multisystem Inflammatory Syndrome in Adults (MIS-A)

Following the emergence of MIS-C in April 2020, descriptions of a similar clinical entity in adults were reported.[187] The CDC case definition for MIS-A was developed in 2021 and includes an illness in patients >/= 21 years with fever for at least 24 h and primary clinical criteria of either severe cardiac illness or rash and non-purulent conjunctivitis and at least two of the following secondary clinical criteria: new-onset neurologic signs and symptoms; shock or hypotension not attributable to medical therapy; abdominal pain, vomiting or diarrhea; or thrombocytopenia (platelet count < 150,000/microliter). In addition, patients must have laboratory evidence of inflammation (elevated CRP, ferritin, IL-6, ESR, or procalcitonin) and a positive SARS-CoV-2 test for current or recent infection. While not fully elucidated, the underlying pathophysiology in MIS-A is felt to involve a dysregulated immune response following COVID-19, as occurs with MIS-C. A systemic review of 53 articles with a total of 79 MIS-A patients in 2022 found that most patients were (mean age 31 years), male (73.2%), with 1/3 having comorbidities, including obesity. In this review, no patients had coronary artery aneurysms compared to roughly 7% in children diagnosed with MIS-C.[188] While treatment protocols have been well-established for MIS-C, consensus on optimal treatment guidelines for MIS-A have not yet been put in place.[189] Practically, clinicians often extrapolate from treatment strategies for MIS-C to aid in the therapy of MIS-A, and the CDC states that it is reasonable to do so at this time. Lastly, although the incidence of MIS-A is relatively rare compared to MIS-C, the mortality rate of MIS-A has been measured at 5–7%[190,191] compared to just 0.09% in one large retrospective cohort study in the United States.[192]

Epidemiology of MIS-C

Incidence

MIS-C is a rare pediatric complication of COVID-19, with an initial incidence in the U.S. of 45 to 54 cases/100,000 SARS-CoV-2 infections in children <15 years old during the peak years of its course.[80,193] MIS-C typically presents 2–6 weeks after SARS-CoV-2 infection, with a sharp decline in the incidence in the U.S. after February 2022, as illustrated by the graph from the CDC (https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance). The incidence of MIS-C has continued to decrease when the incidence of COVID-19 appeared to have reached a steady state (https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance). Determining the true incidence of MIS-C is challenging due to the many contributing factors, including geographic location, prevalent virus strain, patient age, vaccination rates, community level of immunity, and public health measures. The rate of reporting by clinicians greatly affects the calculation of incidence. As home testing became more prevalent, low level infections may not come to medical attention. Additionally, testing may be less readily available in low resource settings in the home or clinical setting, leading to a lower number of reported cases. An appraisal of the epidemiology on a global scale is beyond the scope of this review; the focus here will be the changing landscape of MIS-C since 2020.

Severity of Illness—Acute COVID-19 Versus MIS-C

Efforts to characterize the disease severity of MIS-C have been made by comparing it with that of acute COVID-19. A prospective cohort study of patient encounters at 56 facilities in the U.S. through September 2021 was undertaken by Martin et al[194] This study analyzed patient data from the National COVID Cohort Collaborative and compared 8241 children with acute COVID-19 with 707 children with MIS-C. 818 (10%) of the 8241 children with acute COVID-19 met criteria for severe illness, whereas 261 (37%) out of 707 children with MIS-C met criteria. Of the patients with MIS-C, 117 (17%) required invasive mechanical ventilation, 191 (27%) received vasopressor or inotropic support, < 20 (0%) needed extracorporeal membrane oxygenation (ECMO), and <20 (0%) died or were discharged to hospice. In the COVID-19 cohort, 514 (6%) received invasive mechanical ventilation, 426 (5%) required vasopressor or inotropic support, 25 (0.3%) were on ECMO during hospitalization, and 95 (1%) died or were discharged to hospice. Compared to patients with acute COVID-19, more children with MIS-C had a severe clinical trajectory, with more frequent vasopressor or inotropic support and invasive mechanical ventilation. In this cohort, variables that were associated with increased odds of MIS-C versus acute COVID-19 were: male, Black race, age less than 12 years, obesity, and the absence of preexisting chronic comorbidities.

MIS-C Trends Over Time

Acute MIS-C cases peaked in January and February of 2021, with a sharp decline after February 2022, two to three months after the Omicron variant appeared in the U.S.[68,188,195,196] MIS-C severity has also decreased from 2020 to 2022..[195–200] Sperotto et al[201] performed a multi-center observational retrospective study, interrogating EHR from all patients with MIS-C hospitalized between February 2020 and May 2022 in seven pediatric hospitals in France, Spain, UK, and the U.S. Of 598 patients with MIS-C, 383 (64%) were admitted in the Alpha era, 111 (19%) in the Delta era, and 104 (17%) in the Omicron era. Patients admitted during the Omicron versus the Alpha era were younger, had less frequent occurrence of SIRS, lower lymphocyte count, lower troponin, and less frequent use of anticoagulation therapy. Length of hospitalization was shorter after the Alpha era. Rao et al[202] performed a retrospective review of EHR data of 1139 patients with MIS-C or presumed MIS-C, seen at 8 institutions in the U.S. between March 2020 and September 2022. 41.4% were admitted to the ICU, 16.1% required mechanical ventilation (invasive and non-invasive), and 15 (1.3%) children died. A higher proportion of children had a severe presentation in the earlier phase of the pandemic. 52.3% of children with MIS-C presented with severe illness during the pre-Delta period, versus 39.6% during the post-Delta period. Lopez et al[199,200] reported that the Paediatric Active Enhanced Disease Surveillance (PAEDS) network in Australia[203] (www.paeds.org.au) identified 107 cases of MIS-C from May 2020 to April 2022; with a reduction in cases over time, particularly during the Omicron period, which occurred from December 2021 to April 2022 in Australia. Similar observations were reported from the United Kingdom, Israel, and Denmark.[204–206] It is unclear how global vaccination rates may have contributed to this shift.

The most recent report from the CDC[161] provided a similar picture. MIS-C incidence reported to the CDC in 2023 was 0.11 cases per million person-months, an 80% decline compared with that during April–December 2022 (0.56 cases per million person-months), and a 98% decrease from the peak of 6.79 early in the COVID-19 pandemic (October 2020–April 2021). The median age of MIS-C patients with illness onset in 2023 was 7 years (Table), whereas the median age during February 2020–January 2022 was 9 years, and during April–December 2022 was 5 years. Among the 117 MIS-C patients with illness onset in 2023, 68 (58%) had no underlying medical conditions; 58 (50%) required intensive care unit (ICU)-level care, 40 (34%) experienced shock, and 31 (27%) experienced cardiac dysfunction. The prevalence is similar to published national MIS-C surveillance data for 2116 cases reported during July 9, 2021– January 31, 2022 (52% requiring ICU-level care, 38% with shock, and 29% with cardiac dysfunction), and are improved compared with data for cases reported for the total 4470 cases during the earliest part of the pandemic, from February 19, 2020–July 31, 2021 (63% requiring ICU-level care, 45% with shock, and 31% with cardiac dysfunction)[195,196,207] (https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance; Accessed March 11, 2024).

Snooks et al[192] carried out a retrospective cohort study using the Virtual Pediatric Systems Database including all children with MIS-C admitted to the PICU in 115 hospitals in Canada

and the U.S, between January 2020 and June 2021. Of 145,580 children admitted to the PICU during this period, 1338 children (0.9%) were admitted with MIS-C, with the largest numbers admitted in quarter 1 of 2021 (n = 626). The median PICU LOS was 2.7 days with a median hospital LOS of 6.6 days. 15.2% received mechanical ventilation with a median duration of mechanical ventilation of 3.1 days. There were 11 in-hospital deaths. During the study period, there was a significant decrease in the median PICU and hospital LOS and in the frequency of mechanical ventilation, with the most significant decrease occurring between the quarter 3 and quarter 4 of 2020. The authors postulated that the change was related to improvements in disease recognition and therapeutics rather than to a change in viral strains, since the decline preceded the viral changes, and the original SARS-CoV-2 virus and related strains were predominant through 2020.

Socio-Economic and Racial Disparities in SARS-CoV-2 Infections among Children

A cross-sectional study was conducted by Goyal et al[208] at a U.S. urban SARS-CoV-2 testing site where 1000 children were tested in 2020, found higher infection rates in Hispanic and black children.

Of the 207 positive cases, 46.4% were Hispanic, 30% were Non-Hispanic Black, and 7.3% were White—in a city where the population was 11.3% Hispanic, 46% Non-Hispanic Black, and 46% Non-Hispanic White.[208] Patient- and/or family-reported exposure differed by median family income (MFI), with higher rates of exposure in less socioeconomically advantaged households; one postulated factor being the higher rate of parental occupation with on-site rather than remote work. Positivity rates increased over time among Hispanic children, but not among other racial and/or ethnic groups. Similarly, Javalkar et al[209] undertook a multicenter retrospective case-control study at 3 academic centers in the U.S. in 2020. Their findings indicated that lower socio-economic status (SES) or higher social vulnerability index (SVI), Hispanic ethnicity, and Black race independently increased risk for MIS-C. CDC surveillance data (https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance) also report that Hispanic/Latino and Non-Hispanic Black populations are disproportionately affected by COVID-19, suggesting that additional studies of MIS-C are needed to learn why some racial or ethnic groups may be disproportionately affected and to understand the risk factors for this disease. These studies show that racial and socio-economic disparities remain an imperative healthcare issue.

Outcomes: A Global Perspective

The quantification of outcomes in MIS-C iis challenging, as outcomes are variable globally and domestically. Outcomes during the acute illness of MIS-C have been discussed in conjunction with the therapeutic agents in Section 4; this section will briefly review patient outcomes with a global perspective.

Hoste et al[72] conducted a detailed review of the published literature world-wide with 953 cases from 68 publications in 2020; some countries or institutions would be more heavily represented by virtue of publishing more often. Of the 953 patients, 53% presented with shock, 73% required ICU admission and 3.8% required ECMO. Despite this large aggregate with critically ill patients, the mortality rate remained low at 1.9%. 2 patients had persistent neurological damage following their acute phase of illness. Sik et al[210] undertook a retrospective multicenter cohort study examining 322 children with MIS-C in 41 PICUs in Turkey.[210] Sixteen (5%) of the children died and 8 children had underlying conditions such as cancer or congenital heart defects. Ibrahim et al[76] reported on a cohort of 35 patients who were hospitalized in a PICU in Egypt from June to July 2020. There was a 90.3% survival rate and a mortality rate of. 9.7% The authors pointed out that the high mortality rate is likely due to the late presentation of some patients, as well as to comorbid conditions—the 3 patients who died were subsequently diagnosed with malignancies. Nachega et al[211] conducted a cohort study using a retrospective record review of data from 25 hospitals in the Democratic Republic of the Congo, Ghana, Kenya, Nigeria, South Africa, and Uganda from March to December 2020, including 469 hospitalized patients aged 0 to 19 years with SARS-CoV-2 infection. 18 of 297 cases (6.1%) were clinically suspected (6 patients) or confirmed (12 patients) as having MIS-C. The overall rate of discharge was 89%, with a mortality rate of 8.3%.

The mortality rate may vary significantly within the same country, as illustrated by the following reports from a geographically large country such as Brazil. A multi-institutional study by Lima-Setta et al,[212] which included 56 patients in 17 PICUs in 5 Brazilian states, found that the median length of PICU stay was six days, and one death occurred (1.8%). The authors concluded that these patients shared similar disease and outcome parameters with many other cohorts of patients with MIS-C. In another study, Almeida et al[213] analyzed EMR data from 16 public and private hospitals providing secondary and tertiary care in the metropolitan area of São Paulo, Brazil. 101 patients met the MIS-C criteria and were evaluated. The median age was 67 months, 60% were male, 28.7% were black or afro-descendant and 62.3% were admitted to public hospitals. 16.8% of patients had underlying medical conditions. 43.5% had a Kawasaki disease-like phenotype and a lower median age. Children with severe MIS-C were older (median age 91 months vs 36 months); 73.3% required intensive care, 20.8% required mechanical ventilation and 35.6% required inotropic support. Four deaths occurred (CFR = 3.9%), three of which were in healthy participants.

Farias et al reported on a prospective cohort study with 208 critically ill children and adolescents, with 67 (32.2%) patients in MIS-C group, and 141 (67.8%) patients in the severe COVID-19 group. The patients were admitted to three tertiary pediatric intensive care units in the Brazilian Amazon,

between April 2020 and July 2022. Mechanical ventilation support, cardiogenic shock and acute respiratory distress syndrome occurred in 47%, 30% and 34.1% of patients, respectively; and there were 37 (18%) deaths. The authors postulated that the increased incidence of poor outcomes was a result of the high prevalence of malnutrition (62%) and comorbidities (60.6%). Jiang et al[79] conducted a literature review and meta-analysis of diverse patient populations from both low/middle-income countries and high-income countries and explored the disparities in outcomes. The data indicated that compared to high-income countries, low/middle- income countries had a lower percentage of pediatric MIS-C patients with an ICU admission or on mechanical ventilation, and a much higher mortality rate. Similarly, Irfan et al[214] conducted a metanalysis of 129 case studies from 31 countries comprising 9335 children with COVID-19 associated illness, and compared disease characteristics, management and outcomes according to World Bank country income level, and arrived at the following conclusion: In low-income and middle-income countries (LMIC), a lower proportion of cases were admitted to intensive care units (ICUs) (9.9% vs 26.0%) compared to high-income countries (HIC), yet pooled proportion of deaths among hospitalized children was higher (relative risk 2.14). Among the hospitalized patients, 40 deaths were reported in HICs compared with 56 in LMICs (pooled proportion 2.9% vs 5.2%). Thirty-one studies (n = 1208) with 22 from HIC (n = 602) reported series of children presenting with MIS-C. Nearly half of the children who met MIS-C criteria (638/1208) were admitted to the PICU, and (449/638, 70.3%) of these ICU admissions were patients from HIC, compared with 22.9% in the overall analysis. The authors concluded that the difference in access to intensive care may be is a likely contributor to the mortality difference. These data highlight the challenges faced by clinicians and patients, contingent upon the available resources and the infrastructure for healthcare delivery.

Post Acute Sequelae of MIS-C

Capone et al[215] evaluated 31 patients at 2 weeks, 8 weeks, and 6 months after discharge from inpatient care at a hospital in New York from April to June 2020 with a diagnosis of MIS-C. In the acute phase of MIS-C, 66% of patients had cardiovascular manifestations which included LV systolic and diastolic dysfunction, coronary dilation, and coronary artery aneurysm. At the 2 week follow up, 2 patients reported fatigue with ordinary activity. Although LV function returned to normal for all but one patient who continued with mild dysfunction, and coronary abnormalities were improving, 5 patients continued to have mild diastolic dysfunction. At the 8 week follow-up, 5 patients reported fatigue with ordinary activity, all patients had normal LV function, all coronary aneurysms/dilation had resolved, 4 patients continued with diastolic dysfunction and coronary abnormalities persisted in 5 patients. Patients were then evaluated again at 6 months and were found to be asymptomatic and at their physical baseline. One patient continued to have LV diastolic dysfunction, but all cardiac manifestations resolved in all other pediatric patients who were evaluated for this study.

Kahn et al[216] conducted a national, longitudinal, multicenter study in Sweden, using follow-up data of all patients with MIS-C in the country. All cases were reported to a national registry, and all patients were evaluated as part of a nationally standardized follow-up program which was established in December 2020. Of the 243 cases of MIS-C in Sweden as of May 2021, 177 were seen after the standardized follow-up program was established, and consent was obtained for 133 patients, who were eligible for this study. At 2 weeks after MIS-C was diagnosed, 43% of 119 patients had abnormal results, including complete blood cell counts, platelet counts, albumin levels, electrocardiograms and echocardiograms. At 8 weeks, 36% of 89 had persistent symptoms, with fatigue being the most common complaint; 5% of 67 patients had abnormalities in the echocardiogram.

Maddux et al[217,218] performed a multicenter prospective observational cohort study, with outpatient surveys at 2 to 4 months after admission for 60 children and adolescents who were hospitalized for acute COVID-19 or MIS-C at 25 pediatric hospitals in the U.S. Fatigue or weakness were the most common symptoms in both children with acute COVID-19 and MIS-C, followed by cough and shortness of breath in the acute COVID-19 group, and headache in the MIS-C group. More than 1 in 5 patients with MIS-C were unable to walk or exercise at their previous level. 12 patients (8%) had a re-admission. Rollins et al[105] studied neurological and psychiatric symptoms in 64 patients with MIS-C and 34 healthy controls, evaluated from November 2020 to November 2021 at 6–12 months after hospital discharge in Canada and the U.S. Patients who were hospitalized for MIS-C had more abnormal neurologic examinations, worse working memory performance, more somatization and depression symptoms, and lower quality of life 6 to 12 months after hospital discharge, when compared with siblings or community controls. These studies highlight the need to recognize the potential of persistent impairments after patients have recovered from the acute effects of MIS-C. Recent publications from a number of countries suggest that pediatric long COVID may occur in a small number of children after acute SARS-CoV-2 infection, with most recovering fully over weeks to months.[219–223] Whether long COVID truly occurs after MIS-C, and which strategies would best support patients during the post- MIS-C period, are questions that await answers from further research.

Conclusion

MIS-C emerged in 2020 as a serious pediatric illness that presented several weeks after acute SARS-CoV-2 infection. An improved understanding of its pathophysiology and of the spectrum of response to viral illness has since been attained. There is still much to be learned regarding the mechanisms and susceptibilities that lead to MIS-C and the potential for persistent dysfunction and development of long COVID in its wake.

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OS, NA, SVB, KAG, LH, SAM, SAO, PHY, JL—writing
SVB, RWC, OS, PHY, JL—editing
RWC, VM, LMY, JL- content review
JL—design, planning, organization, revisions
All authors approve of submission of the manuscript for publication.

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