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Review

Emerging Insights Into the Pathophysiology of Multisystem Inflammatory Syndrome Associated With COVID-19 in Children

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) has emerged as a rare delayed hyperinflammatory response to SARS-CoV-2 infection and causes severe morbidity in the pediatric age group. Although MIS-C shares many clinical similarities to Kawasaki disease (KD), important differences in epidemiologic, clinical, immunologic, and potentially genetic factors exist and suggest potential differences in pathophysiology and points to be explored and explained. Epidemiologic features include male predominance, peak age of 6 to12 years, and specific racial or ethnicity predilections. MIS-C is characterized by

RÉSUMÉ

Le syndrome inflammatoire multisystémique de l'enfant (SIME) qui s'est révélé une réponse hyperinflammatoire tardive rare à l'infection SRAS-CoV-2 cause une morbidité grave chez les enfants. Bien que le SIME ait en commun plusieurs similarités cliniques avec la maladie de Kawasaki (MK), d'importantes différences dans les facteurs épidémiologiques, cliniques, immunologiques et potentiellement génétiques existent et suggèrent des différences potentielles dans la physiopathologie, et des points à explorer et à expliciter. Les caractéristiques épidémiologiques sont les suivantes : la prédominance

Coronavirus disease 2019 (COVID-19) is the direct clinical manifestation of acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Even from the early days of the pandemic, it has been clear that acute COVID-19 in children is often milder and carries a better prognosis compared with adults.[1] In mid-2020, a novel syndrome with clinical similarities to Kawasaki disease (KD) was first described in children in the United Kingdom, France, Italy, and the United States.[2-5] This condition, now referred to as multisystem inflammatory syndrome in children (MIS-C), is characterized by acute systemic inflammation and multiorgan dysfunction. Epidemiologic data have demonstrated a temporal association between MIS-C and SARS-CoV-2 infection, with MIS-C presenting 3 to 6 weeks after SARS-CoV-2 infection, often asymptomatic in children.[6,7] The majority of patients also possess neutralizing antibodies specific for

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fever, prominent gastrointestinal symptoms, mucocutaneous manifestations, respiratory symptoms, and neurologic complaints, and patients often present with shock. Cardiac complications are frequent and include ventricular dysfunction, valvular regurgitation, pericardial effusion, coronary artery dilation and aneurysms, conduction abnormalities, and arrhythmias. Emerging evidence regarding potential immunologic mechanisms suggest that an exaggerated T-cell response to a superantigen on the SARS-CoV-2 spike glycoprotein—as well as the formation of autoantibodies against cardiovascular, gastrointestinal, and endothelial antigens—are major contributors to the inflammatory milieu of MIS-C. Further studies are needed to determine both shared and distinct immunologic pathway(s) that underlie the pathogenesis of MIS-C vs both acute SARS-CoV-2 infection and KD. There is evidence to suggest that the rare risk of more benign mRNA vaccine-associated myopericarditis is outweighed by a reduced risk of more severe MIS-C. In the current review, we synthesize the published literature to describe associated factors and potential mechanisms regarding an increased risk of MIS-C and cardiac complications, provide insights into the underlying immunologic pathophysiology, and define similarities and differences with KD.

masculine, le groupe d'âge le plus touché (de 6 à 12 ans), et les prédispositions raciales et ethniques particulières. Le SIME est caractérisé par de la fièvre, des symptômes gastro-intestinaux marqués, des manifestations mucocutanées, des symptômes respiratoires et des plaintes neurologiques, et les patients sont souvent en état de choc. Les complications cardiaques fréquentes sont les suivantes : la dysfonction ventriculaire, la régurgitation valvulaire, l'épanchement péricardique, la dilatation coronaire et les anévrismes, les anomalies de conduction et les arythmies. De nouvelles données probantes en ce qui concerne les mécanismes immunologiques potentiels suggèrent que la réponse excessive des cellules T à un superantigène sur la glycoprotéine spiculaire du SRAS-CoV-2 ainsi que la formation des autoanticorps contre les antigènes cardiovasculaires, gastro-intestinaux et endothéliaux sont les principaux facteurs qui contribuent au milieu inflammatoire du SIME. D'autres études sont nécessaires pour déterminer la ou les voies immunologiques partagées et distinctes qui sous-tendent la pathogenèse du SIME *vs* l'infection SRAS-CoV-2 et la MK. Des données probantes suggèrent que le rare risque de myopéricardite plus bénigne associée au vaccin à ARNm l'emporte sur la réduction du risque d'un SIME plus grave. Dans la présente revue, nous faisons la synthèse de la littérature publiée afin de décrire les facteurs associés et les mécanismes potentiels en ce qui concerne le risque accru de SIME et de complications cardiaques, donnons un aperçu de la physiopathologie immunologique sous-jacente et définissions les similarités et les différences avec la MK.

SARS-CoV-2, including high titers of immunoglobulin G (IgG).[6] Insights into the pathophysiology underlying this delayed inflammatory process are emerging and are the focus of this review (Fig. 1).

MIS-C Case Definition

Investigations regarding pathophysiology must first begin with accurate and specific case ascertainment to prevent misclassification. The case definition for MIS-C established by the World Health Organization (WHO) early in the pandemic is summarized in Table 1. This definition was adopted by the Public Health Agency of Canada with an expansion to include patients without a COVID-19 diagnosis, as polymerase chain reaction (PCR) testing may be falsely negative late in the course of infection or—particularly early in the pandemic—caused by limited access to COVID-19 testing: specifically, serology.[8] The definition from the US Centers for Disease Control and Prevention (CDC) differs somewhat from the WHO in extending the age to 20 years; the greater specification of fever and inflammatory markers; and the addition of respiratory, renal, neurologic, and dermatologic involvement as additional organ systems involved (https://www.cdc.gov/mis/mis-c/hcp/).[9] Both the WHO and the CDC recognized that patients may also meet diagnostic criteria for complete and incomplete KD.[10] In contrast, MIS-C has been referred to as Paediatric Multisystem Inflammatory Syndrome (PMIS) temporally associated with COVID-19 in the United Kingdom, and a case definition from the Royal College of Paediatrics and Child Health differs from the WHO and CDC definitions by requiring involvement of only 1 organ and stating that "SARS-CoV-2 PCR testing may be positive or negative" and not including a requirement for evidence of a preceding COVID-19 infection (https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance). Given the clinical overlap with KD, for many patients with MIS-C, the only differentiating feature may be this evidence of previous infection. However, as the pandemic has progressed, and a greater proportion of the population has had previous COVID-19 or has been vaccinated, this evidence may be less conclusive (particularly for serologic evidence of infection, which may not be temporally related), and there have been calls to exclude this requirement from case definitions.[11] This will likely impede research into the pathogenesis, given the potential for misclassification. However, there is hope that the development of machine-learning algorithms, potentially incorporating multiomics (concomitant personalized data from analysis of the microbiome, genome, epigenome, transcriptome, and proteome), which may allow for more accurate diagnosis without the requirement for evidence of previous COVID-19.[12]

Epidemiologic Features

Pathophysiological models should explain the epidemiologic and clinical features of MIS-C, including differences with similar known conditions. These are summarized in Table 2 in comparison with KD. Male sex, peak age from 6 to 12 years and Black and Hispanic race or ethnicity are factors associated with development of MIS-C, with male preponderance also possibly associated with a greater risk of cardiac complications.[13] It is incompletely known whether the male preponderance is due to a greater predilection for SARS-CoV-2 infection or a greater predilection to develop MIS-C given infection. The angiotensin-converting enzyme 2 gene (ACE2), which encodes the receptor used for SARS-CoV-2 entry, is located on the X chromosome and downregulated

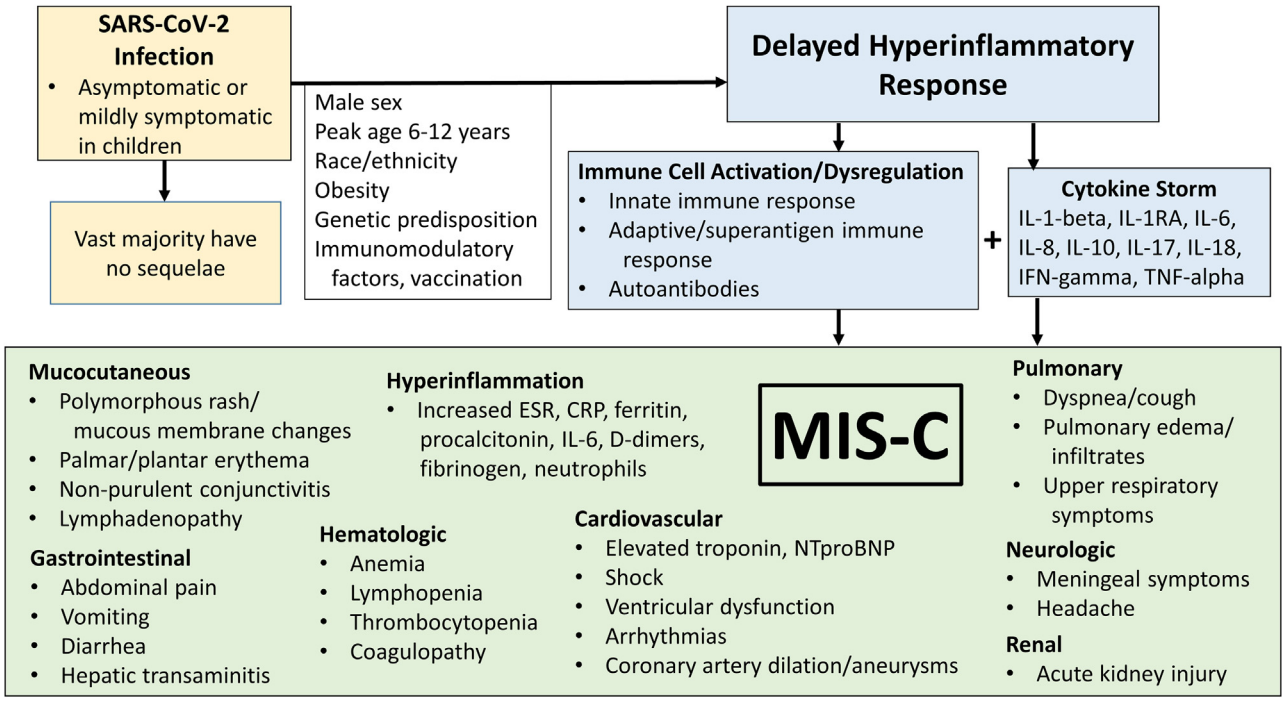

Figure 1. Pathophysiology and clinical manifestations of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; NTproBNP, N-terminal pro-hormone B-type natriuretic peptide; RA, receptor antagonist; TNF, tumour necrosis factor.

by estrogen, predisposing male patients to infection[14-16] and impaired viral clearance and prolonged duration of SARS-CoV-2 detection after infection.[16,17] Regarding predilection for MIS-C, immune function is influenced by sex-related genetic differences, increasing susceptibility for male patients toward inflammatory diseases[18,19] and by sex-related differences in levels of testosterone, estrogen, and progesterone.[14,20-22] Children aged 6 to 12 years are most at risk of MIS-C and more severe outcomes,[4,9,13,23-28] which, although incompletely understood, may be related to age-related differences in ACE2 expression[29] or severity of inflammation.[30] There appears to be an Hispanic and non-Hispanic Black race-ethnicity predominance among patients with MIS-C.[23,26-28,31,32] Although race- and ethnicity-related differences regarding geographic factors and social determinants of health influencing risk of SARS-CoV-2 exposure may be at play,[33,34] Black and Hispanic children have a higher incidence of MIS-C per SARS-CoV-2 infection, even after adjustments for socioeconomic status.[32,35,36] Further epidemiologic and mechanistic studies are needed to elucidate the nature of these associations.

Genetic Predisposition

Race and ethnicity predisposition may suggest a contributing role of host genetics in the development of MIS-C.[37] Early studies exploring genetic associations with MIS-C identified haploinsufficiency of suppressor of cytokine signalling 1 (SOCS1), which functions as a negative regulator of type I and type II interferon (IFN) signalling, as a risk factor.[38] A further study linked MIS-C with hemizygous defects in X-linked inhibitor of apoptosis (XIAP) and CYBB, which encodes the beta subunit of cytochrome b-245.[39] Whole exome sequencing of 45 patients with MIS-C of primarily Arab and Asian origin revealed the presence of rare heterozygous variants in immune-related genes TLR3, TLR6, IFNB1, IFNA6, and IL22RA2 in 19 patients, which were linked to earlier disease onset and resistance to treatment.[40] Heterozygous missense mutations in primary hemophagocytic lymphohistiocytosis (pHLH) genes and the HLH-associated dedicator of cytokinesis 8 (DOCK8) gene may increase risk of MIS-C.[41] The combination of 3 human leukocyte antigen (HLA)-I alleles—specifically, HLA-A*02, B*35, and C*04—may contribute to susceptibility to MIS-C.[42,43] Genetic influences on immunologic pathways specific to MIS-C require further study.

Cardiovascular Involvement

Although cardiovascular involvement—specifically, ventricular dysfunction and coronary artery dilation-aneurysms—is the predominant morbidity of MIS-C, the underlying mechanism remains incompletely understood. The pathophysiology may be multifactorial, potentially including direct injury to cardiomyocytes from SARS-CoV-2 viral invasion and the impact of a dysregulated immune response, leading to microvascular dysfunction and endothelial injury.[44,45] SARS-CoV-2, like other betacoronaviruses, shows tropism to myocardial and endothelial cells.[46] Dolhnikoff et al. reported the case of an 11-year-old girl with MIS-C who died from cardiac failure.[47] An ultrasound-guided minimally invasive autopsy demonstrated myocarditis, endocarditis, and

Table 1. MIS-C case definition from the World Health Organization*

MIS-C diagnosis requires all of the following 4 criteria to be met:
Children and adolescents 0 to 19 years of age with fever for ≥ 3 days
1. Clinical signs of multisystem involvement (at least 2 of the following):
• Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
• Hypotension or shock
• Cardiac dysfunction, pericarditis, valvulitis, or coronary artery abnormalities (including echocardiographic findings or elevated troponin-brain natriuretic peptide)
• Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
• Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
2. Elevated markers of inflammation (eg, ESR, C-reactive protein or procalcitonin)
3. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
4. Evidence for SARS-CoV-2 infection, any of the following:
• Positive SARS-CoV-2 RT-PCR
• Positive serology
• Positive antigen test
• Likely contact with an individual with COVID-19

ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcription-polymerase chain reaction.

*World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: Scientific Brief. 2020. Available at:https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19; accessed May 17, 2020.

pericarditis. SARS-CoV-2 was also detected in cardiac tissue, including cardiomyocytes, endothelial cells, inflammatory cells and mesenchymal cells. A more in-depth autopsy study included 5 patients who died with COVID-19, 3 of whom had MIS-C.[48] In all patients, SARS-CoV-2 was detected in the heart, lungs, and kidneys. Two of the patients with MIS-C had SARS-CoV-2 antigen in endothelial cells of the heart and brain. The third patient with MIS-C, who suffered cardiac failure, was found to have SARS-CoV-2 antigen in cardiomyocytes and in the cardiac endothelium, together with diffuse perivascular interstitial inflammatory infiltrate, severe myocarditis, and cardiac necrosis. These limited data suggest a role for direct SARS-CoV-2 viral invasion producing cardiac involvement, although given that these few patients had severe and fatal disease, the applicability to the majority of patients with MIS-C is unknown. In contrast, case series that have incorporated cardiac magnetic resonance imaging (cMRI) with tissue characterization have noted more myocardial edema, with the majority not meeting criteria for myocarditis, and little myocardial fibrosis as indicated by persistence of late gadolinium enhancement in a minority.[49,50] These data suggest that myocyte necrosis may not be a prominent feature in the majority, despite the clinical finding of elevated cardiac biomarkers and depressed ventricular function during the acute illness.

Immunology

Hyperinflammation is a hallmark of MIS-C. Studies have consistently reported an elevation in inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, procalcitonin, and IL-6.[23,24,51] Other findings include elevated white blood cell count with neutrophilia and lymphopenia, elevated D-dimer and fibrinogen, and elevated myocardial injury markers such as troponin and brain natriuretic peptide (BNP).[23,24] Differences in the laboratory profile of MIS-C compared with acute COVID-19 have been reported. Feldstein et al. reported that patients with MIS-C have higher levels of CRP and a greater neutrophil-to- lymphocyte ratio compared with those with acute COVID-19, as well as a lower platelet count.[27] A systematic review and meta-analysis representing 787 patients with MIS-C noted similar findings.[30] Patients with MIS-C had higher CRPs, absolute neutrophil counts, and D-dimers, as well as lower absolute lymphocyte counts vs non-severe acute COVID-19. When compared with severe COVID-19, those with MIS-C had higher ESRs and lower platelets and lactate dehydrogenase (LDH) levels. These findings have led to a focus on the immune response and immune dysregulation as the primary drivers of the pathophysiology of MIS-C.

Cytokines

A plethora of cytokines have been found to be elevated in the context of MIS-C, including IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-17, IL-18, IFNγ, and tumour necrosis factor (TNF)α.[52-57] Some have also identified increases in CCL3, CCL4, CCL20, CCL28, and CDCP1.[56] Although the relative contributions of these cytokines is still unclear, it appears that IFNγ, IL-10, and TNFα are particularly elevated and may have important roles in the pathogenesis of MIS-C.[53] A prospective study of 14 patients with MIS-C found that the cytokine storm of MIS-C is characterized by IFNγ as a central mediator as opposed to type I IFN, which is enhanced in severe acute COVID-19.[57] This finding is further supported by the observation that CXCL9 and CXCL10, which are signature cytokines of IFNγ, are elevated in MIS-C.[57,58] Diorio et al. also found disproportionately high levels of CXCL9, indicating a dysregulated IFNγ response.[59] A recent longitudinal multicentre study of 110 children with acute COVID-19,—76 with MIS-C and 76 healthy controls with multiomic profiling (single-cell gene expression, proteomics, soluble biomarkers, immune repertoire analysis)—demonstrated strong type I IFN responses in acute COVID-19, whereas MIS-C was characterized by type II IFN- and NF-κB-dependent signatures, elevated levels of circulating spike protein, and matrisome activation.[43]

Table 2. Comparison of MIS-C vs Kawasaki disease

	MIS-C	Kawasaki disease
Demographics		
Sex	Male patients at slightly higher risk	Male patients at greater risk (~1.5:1)
Age	Most likely in children aged 6-12 years (median age 8-9)	Primarily children < 5 years old (median age 3)
Race/ethnicity	Hispanic and non-Hispanic Black at highest risk	Asian and Pacific Islanders, particularly those with Japanese ancestry, at highest risk
Etiology		
Causative agent	SARS-CoV-2 infection 3-6 weeks before	Unknown; environmental and infectious exposures have been proposed
Clinical		
Similarities	Fever, rash, bilateral bulbar conjunctival injection, cervical lymphadenopathy	
Differences	• Gastrointestinal symptoms more common • Neurologic symptoms more common • Admission to intensive care unit more common • Higher case fatality rate	• Oral mucous membrane changes more common
Laboratory		
Similarities	Elevated WBC counts, CRP, and ESR	
Differences	• Higher CRP • Higher procalcitonin • Higher ferritin • Lymphopenia • Thrombocytopenia • Higher troponin • Higher BNP, NT-proBNP • Higher D-dimer	• Thrombocytosis (later sign) • Monocytosis (?)
Immunology		
Similarities	• Increases in IL-1RA, IL-1β, IL-6, IL-18, TNF-α • IL-15/IL-15RA-centric cytokine storm • Autoantibodies directed toward endothelial antigens • Complement activation	
Differences	• Potential superantigen mechanism with polyclonal expansion of TCR Vβ 21.3+ CD4+ and CD8+ T cells • Lower levels of naïve CD4+ T cells and follicular helper T cells • Higher levels of central memory and effector memory CD4+ T cells • IL-1RA autoantibodies	• T-cell activation by conventional antigen • Marked elevation of IL-17A • Autoantibodies against EDIL3 • Autoantibodies against DEL-1
Cardiovascular complications		
Similarities	• Risk for coronary artery abnormalities (dilatation/aneurysm) • Risk for myocarditis (usually myocardial edema rather than necrosis) • Risk for ECG changes (eg, PR interval prolongation, ST segment changes, T-wave changes) • Risk for valvular regurgitation	
Differences	• Higher likelihood of ventricular dysfunction	• Coronary artery sequelae can be serious and long-lasting
Genetics		
Associated genes	SOCS1 XIAP CYBB TLR3 TLR6 IFNB1 IFNA6 IL22RA2 DOCK8 HLA-I alleles: HLA-A*02, B*35 and C*04	CASP3 BLK FCGR2A ITPKC TGFβ2, TGFβR2, SMAD3 (increased risk of aneurysm formation) CD40 HLA-II

BNP, B-type natriuretic peptide; CRP, C-reactive protein; DEL1, developmental endothelial locus-1; DOCK8, dedicator of cytokinesis 8; ECG, electrocardiographic; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal-proB-type natriuretic peptide; SOCS1, suppressor of cytokine signalling 1; TCR, T-cell receptor; TGF, transforming growth factor; TNF, tumour necrosis factor; WBC, white blood cell.

Innate Immune System

MIS-C is associated with a number of features reflective of participation of the innate immune system. Patients with MIS-C have a decrease in monocyte count, as well as a profound depletion of plasmacytoid dendritic cells.[53,58] The cells that remain exhibit various forms of dysfunction. Carter et al. reported activation of neutrophils and monocytes during the acute phase of MIS-C, as demonstrated by high CD64 expression.[52] This observation is consistent with another study that found both CD54 and CD64 to be upregulated in neutrophils and monocytes.[56] In addition, antigen-presenting cells—including monocytes, dendritic cells, and B cells—have been noted to have low expression of CD86 and HLA-DR, which is suggestive of impaired antigen-presentation ability.[52,54] Monocyte profiling may be helpful in differentiating MIS-C from acute COVID-19, given that patrolling monocytes dominate in MIS-C, whereas HLA-DR^{lo} classical monocytes are more abundant in severe COVID-19.[57] Complement activation is thought to occur in a subset of patients with MIS-C, as evidenced by elevated levels of soluble

C5b-9 (the membrane attack complex).[6,57,60] McCafferty et al. conducted a study using mass spectrometry proteomics and hypothesized that in MIS-C complement activation is induced via the lectin pathway.[61]

T cells (superantigen hypothesis)

T-cell lymphopenia is consistently observed in MIS-C and encompasses CD4+, CD8+, and γδT cells.[6,52,53,62] In MIS-C, there are significantly lower numbers of CD8+ T cells compared with children with only mild acute SARS-CoV-2 infection.[7] Of the remaining cells, a large portion express CD38 and the major histocompatibility complex (MHC) class II receptor HLA-DR, indicating T-cell activation.[53,54,57,62] There is significant clinical overlap between MIS-C and toxic shock syndrome (TSS), which is most commonly triggered by bacterial superantigens such as staphylococcal enterotoxin B and streptococcal mitogenic exotoxin Z. In TSS, exposure to the superantigen results in widespread T-cell activation and massive proinflammatory cytokine release that culminates in multiorgan tissue injury, as seen with MIS-C.[42,63] The similarities between these 2 conditions has prompted the consideration of a superantigen as a trigger for MIS-C. This hypothesis is supported by 2 key observations: the discovery of a superantigen-like motif on SARS-CoV-2 and the expansion of T cells expressing T-cell receptor (TCR) beta variable gene 11−2 (TRBV11-2), encoding Vbeta(Vβ)21.3 in patients with MIS-C. First, using structure-based computational models, Cheng et al. identified a polybasic high-affinity motif for binding TCRs on the SARS-CoV-2 spike glycoprotein. This epitope closely resembles the bacterial superantigen Staphylococcal enterotoxin B with respect to both sequence and structure and is not found in the spike proteins of betacoronaviruses apart from SARS-CoV-2. A rare mutation found in a European strain of the virus, D839Y, enhanced the interaction between SARS-CoV-2 and human T cells.[63] Second, studies have consistently demonstrated an expansion of Vβ21.3+ T cells in patients with MIS-C.[42,43,54,57,64] Vβ21.3, encoded by TRBV11-2, contains polyacidic residues that interact strongly with the superantigen-like motif of the SARS-CoV-2 spike glycoprotein.[42] A study of 4 patients with mild and 16 with severe MIS-C showed that TRBV11-2 T cells comprised up to 24% of the clonal T cell space. This expansion correlated with both serum cytokine levels and MIS-C severity, which is consistent with an immune response triggered by a superantigen.[42] Moreews et al. found that 75% of patients with MIS-C displayed an expansion of activated Vβ21.3+ T cells in both CD4 and CD8 subsets, a phenomenon that was not observed in individuals with acute COVID-19, KD, or TSS.[54] Hoste et al. also observed a skewed TCRβ repertoire enriched for TRBV11-2 in all 14 patients with MIS-C in their cohort.[57] The presence of a putative high-affinity binding motif for TCRs on the SARS-CoV-2 spike glycoprotein, in combination with the profound expansion of Vβ21.3+ T cells seen in patients, provides compelling evidence for the role of a superantigen mechanism in the pathogenesis of MIS-C.

Multiple other abnormalities in T-cell biology have been proposed as contributors to the pathogenesis of MIS-C. Natural killer (NK) cells and CD8+ T cells are 2 cytotoxic cells of the immune system that can regulate each other in the context of a viral infection. NK cells play a key role in a process known as CD8+ T-cell exhaustion, which can ameliorate inflammatory disease symptoms. However, abnormalities in NK and CD8+ T cell biology identified in MIS-C include a depletion of NK cells as well as dysregulation of the ones that remain. This could disrupt CD8+ T-cell exhaustion, leading to the inflammatory milieu seen in MIS-C.[65] Moreover, in their analysis of soluble biomarkers in patients with MIS-C, Sacco et al. discovered low levels of CCL22, an important mediator of T-cell homeostasis.[43] CCL22 is a chemokine that promotes function and migration of regulatory T cells. Reduced CCL22 may result in a diminished regulatory T-cell response, leading to unchecked inflammation. Another feature of the immune response of patients with MIS-C that distinguishes it from pediatric COVID-19 is the activation of vascular patrolling CX3CR1+ CD8+ T cells.[62] CX3CR1 is a chemokine receptor that binds the ligand CX3CL1, and this ligand-receptor interaction has been found to have a role in cardiovascular disease. CX3CL1 expression can be increased in the vasculature in cardiovascular conditions, resulting in recruitment of CX3CR1-expressing cytotoxic T cells. This CX3CR1-CX3CL1 axis, therefore, may represent a mechanism for the vascular pathology observed in MIS-C. Overall, these findings suggest that aberrancies in the T-cell response may be an important underlying factor in the pathogenesis of MIS-C.

B cells, antibodies, autoantibodies

It has been shown that patients with MIS-C mount an appropriate antibody response to SARS-CoV-2.[6,7,53,56] Despite the presence of neutralizing antibodies specific for SARS-CoV-2, there are numerous anomalies in B-cell biology that are thought to contribute to pathogenesis of MIS-C. Hoste et al. characterized the B-cell populations of MIS-C vs severe acute COVID-19.[57] They found pronounced expression of CD86 in patients with MIS-C, particularly in severe cases. There was also downregulation of both HLA-DR and CD25 in MIS-C, whereas only HLA-DR expression was decreased in severe COVID-19. The blood of patients with MIS-C has been found to have lower levels of total, effector, and memory B cells compared with healthy counterparts[6,52] as well as increased levels of circulating plasmablasts.[53] These plasmablasts are short-lived and may secrete antibodies directed against self-antigens.[64] There is likely a significant autoimmune component underlying the pathogenesis of MIS-C. Patients with MIS-C have been found to have both IgG and IgA autoantibodies against cardiovascular, gastrointestinal and endothelial antigens.[6,7,53,56] Gruber et al. noted the presence of anti-La autoantibodies in patients with MIS-C, which also have known associations with autoimmune diseases. These autoantibodies may interact with CD64 (also known as the high-affinity human IgG receptor FcγR1) to trigger inflammation and tissue injury.[56] Further evidence for this comes from the observation that CD64 is overexpressed in activated neutrophils and monocytes in MIS-C.[6,52,66] A study including 7 patients with mild and 20 with severe MIS-C demonstrated a strong autoimmune signature.[67] Autoantibodies against a wide variety of targets were detected, including antigens in the gastrointestinal tract (eg, ATPase H+/K+-transporting α subunit, abbreviated ATP4A),

cardiovascular tissue (eg, PDZ and LIM domain 5, abbreviated PDLIM5), brain tissue (eg, microtubule-associated protein 9, abbreviated MAP9), and skeletal muscle (eg, RNA-binding motif protein 38 [abbreviated as RBM38]). Other specific autoantibody targets that have been identified in MIS-C include endoglin, IL-1RA, and proteins involved in signal transduction, including MAP2K2, CSNK1A1, CSNK2A1, and CSNK1E1.[7,68] Endoglin is a glycoprotein expressed by endothelial cells, particularly the vascular endothelium, and is essential for the structural integrity of arteries.[7] Finally, in a recent multicentre retrospective cohort study, 13 of 21 (62%) patients with MIS-C were found to have autoantibodies against IL-1RA.[68] The authors proposed that the autoantibodies may have been generated because of the presence of a hyperphosphorylated, aberrant isoform of IL-1RA. These anti-IL-1RA antibodies impaired IL-1RA bioactivity, which may contribute to the excessive IL-1β signalling observed in MIS-C. Taken together, these findings are highly suggestive of an autoimmune component to the pathogenesis of MIS-C.

Associations with previous vaccination and infection

COVID-19 mRNA-based vaccines may have a significant protective effect against the development of MIS-C. One French study found that, compared with unvaccinated adolescents, those who had received 1 dose of vaccine had a hazard ratio for MIS-C of 0.09.[69] These results are consistent with a large-scale US study conducted in hospitalized patients aged 12 to 18 years across 20 states.[70] Using a test-negative case-control design, patients with MIS-C had decreased likelihood of vaccination, with an adjusted odds ratio of 0.16, with 92% of vaccine-eligible patients being unvaccinated. A prospective population-base cohort study in Denmark during the period dominated by the Delta variant reported an estimated vaccine effectiveness of 94% against the development of MIS-C.[71] The incidence of MIS-C was 1 in 3400 among unvaccinated individuals and 1 in 9900 among those vaccinated who had breakthrough infections, suggesting that the reduction in MIS-C might be caused by a combination of reduced infection and a reduced risk of MIS-C in the setting of breakthrough infection.

Given the known association of mRNA vaccination with rare cases of acute myopericarditis,[72] concerns have been raised regarding the possibility of MIS-C following vaccination. Ouldali et al. described 12 patients aged 12 to 16 years with a clinical picture consistent with MIS-C (all met WHO criteria) occurring 2 to 42 days after their latest mRNA COVID-19 vaccination.[73] Using population-based surveillance, this gave an incidence of 2.9 per 1,000,000 vaccinated children aged 12 to 17 years compared with an incidence of MIS-C of 113 per 1,000,000 children of the same age group who were infected with SARS-CoV-2, favouring vaccination. A similar US-based surveillance study identified 21 cases of MIS-C after vaccination, 15 of whom had evidence of previous infection.[74] This gave an incidence of 1 MIS-C case per 1,000,000 vaccinated adolescents (0.3 cases if restricted to those without previous infection), significantly lower than the incidence of approximately 200 cases of MIS-C per 1,000,000 SARS-CoV-2 infections among unvaccinated adolescents.[35] Although vaccination may be a rare cause of MIS-C, this risk is outweighed by the benefit of vaccination in preventing MIS-C, probably by preventing infection and preventing MIS-C given breakthrough infection.

MIS-C and KD

KD is an acute vasculitis that primarily affects children below 5 years of age, with coronary artery aneurysms being the most important complication occurring in ∼25% of untreated patients.[10] Similar to MIS-C, the diagnosis of KD rests on the presence of clinical criteria that have changed little since the original description. Although the trigger for MIS-C is known, being SARS-CoV-2 infection, the trigger(s) for KD remains elusive, although coronavirus has been possibly implicated in specific outbreaks in the past.[75] Similarities and differences regarding epidemiologic and clinical features, and a predilection for cardiovascular involvement, have suggested some shared pathophysiology (Table 2).[76] KD has been considered the leading cause of acquired heart disease in children for many years, but it has been overtaken by MIS-C during the current COVID-19 pandemic era.[77] Another interesting observation is that during period of pandemic mitigation strategies, such as masking, social distancing, and lock-down measures, there has been a decrease in the incidence of KD.[53,78] It is possible that some of the decrease in KD may be related to misclassification of KD patients as having MIS-C, although this is more likely related to decrease exposure to possible infectious or environmental triggers.[79,80] A case series from Korea, where the incidence of MIS-C during the pandemic has been very low, compared 19 KD patients with a history of previous COVID-19 with 26 patients with KD without COVID and noted few differences, although patients with previous COVID were older with more severe disease, which may suggest some similarities with MIS-C.[81] The association of previous COVID-19 and vaccination with the risk of subsequent KD is largely unknown. In contrast, a report from Seattle noted that patients with previous histories of KD did not have adverse outcomes when either infected with SARS-CoV-2 or vaccinated with mRNA COVID-19 vaccines.[82]

Given the clinical overlap, the immunologic mechanisms proposed underlying the pathophysiology of MIS-C vs KD are of increased interest, with the hope that insights for one condition may shed light on the other. There are conflicting opinions in the literature: Some believe that MIS-C and KD are on the same continuum, whereas others argue that they are distinct entities. There are important similarities in the immunologic profiles of the 2 syndromes. Both KD and MIS-C have comparable proinflammatory signatures, including increases in IL-1RA, IL-1β, IL-6, IL-18, and TNF-α.[45,54,56,57,60,83,84] Other shared features include the presence of autoantibodies against endothelial cell antigens[7,45,56] and activation of the complement system.[6,45,57,60] One recent study has provided convincing evidence suggesting that MIS-C and KD share proximal pathways of immunopathogenesis.[85] Using an artificial intelligence-based approach, Ghosh et al. found that both syndromes are characterized by a cytokine storm centering on IL-15/IL-15RA. They posit that MIS-C and KD exist on the same continuum of the host immune response, with MIS-C positioned further on the spectrum of severity.

There are many differences in the immune responses of the 2 conditions. MIS-C appears to be associated with markedly

elevated IL-10,[60] and some patients have higher concentrations of IFNγ-induced CXCL9[84] compared with KD. In contrast, a distinct feature of KD is a strong type 17 T helper-cell response that drives IL-17A-mediated hyper-inflammation.[7,45,83] Whereas a superantigen mechanism is thought to play an important role in the pathogenesis of MIS-C (as described in depth earlier), the current evidence favours an immune response to a conventional antigen in KD.[10,45] MIS-C is also characterized by an expansion of Vβ21.3+ T cells, which distinguishes it from KD.[53,54] Consiglio et al. described a number of differences in T-cell subsets between the 2 conditions: Patients MIS-C were found to have lower levels of naïve CD4+ T cells and follicular helper T cells but higher levels of central memory and effector memory CD4+ T cells compared with patients with KD.[7] Another study demonstrated that patients with MIS-C had a higher proportion of HLA-DR+ CD4+ T cells compared with KD.[52] Finally, although both syndromes have autoimmune components, the specific autoantibodies differ. KD has been associated with autoantibodies against DEL-1[83] and EDIL3,[7] which are proteins that normally function to limit vascular inflammation. Autoantibodies against proteins of the casein kinase family[7,83] and IL-1RA[68] are unique to MIS-C. In summary, there is currently no consensus as to whether or not MIS-C and KD represent distinct immunopathogenic illnesses or if they are 2 syndromes on the same continuum of the host-immune response. Further investigations are likely ongoing.

Conclusions

The emergence of the novel and clinically important condition MIS-C associated with previous COVID-19 in children, together with the pivot during the pandemic to prioritize research and publication associated with COVID-19, has created a rapid and unprecedented understanding of the underlying pathophysiology. Although the hope is that the relevance of this pandemic will die out, the detailed understandings achieved will likely find some applicability to other immune conditions, most notably Kawasaki disease, a condition that has remained largely an enigma and for which therapy has been largely empiric. Any comprehensive understanding must explain epidemiologic, clinical, genetic, pathologic, and immunologic features, and—in addition—incorporate mediating factors such as the microbiome, environment, and social determinants of health. Likewise, understanding disease mechanisms might lead to more specific and targeted diagnostic tests and treatments and perhaps the prospect of prevention. Advances in research methods, including artificial intelligence and machine learning, will likely bring new insights into the complex interplay of factors underlying the pathophysiology of MIS-C.

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References

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica 2020;109:1088-95.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.
3. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771-8.
4. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med 2020;383:334-46.
5. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142:429-36.
6. Henderson LA, Yeung RSM. MIS-C: early lessons from immune profiling. Nat Rev Rheumatol 2021;17:75-6.
7. Consiglio CR, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183:968-981.e967.
8. Laverty M, Salvadori M, Squires SG, et al. Multisystem inflammatory syndrome in children in Canada. Can Commun Dis Rep 2021;47:461-5.
9. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. J Pediatr 2020;226:45-54.e41.
10. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.
11. Rhys-Evans S. Call for a universal PIMS-TS/MIS-C case definition. Arch Dis Child 2022;107:e10.
12. Lam JY, Shimizu C, Tremoulet AH, et al. A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Kawasaki disease in the USA: a retrospective model development and validation study. Lancet Digit Health 2022;4:e717-26.
13. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 2021;5:323-31.
14. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020;20:442-7.
15. Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 2020;318:L1280-1.
16. Stilhano RS, Costa AJ, Nishino MS, et al. SARS-CoV-2 and the possible connection to ERs, ACE2, and RAGE: focus on susceptibility factors. FASEB J 2020;34:14103-19.
17. Shi D, Wu W, Wang Q, et al. clinical characteristics and factors associated with long-term viral excretion in patients with severe acute respiratory syndrome coronavirus 2 infection: a single-center 28-day study. J Infect Dis 2020;222:910-8.
18. Maan AA, Eales J, Akbarov A, et al. The Y chromosome: a blueprint for men's health? Eur J Hum Genet 2017;25:1181-8.

19. Case LK, Wall EH, Dragon JA, et al. The Y chromosome as a regulatory element shaping immune cell transcriptomes and susceptibility to autoimmune disease. Genome Res 2013;23:1474-85.

20. Furman D, Hejblum BP, Simon N, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc Natl Acad Sci USA 2014;111:869-74.

21. Straub RH. The complex role of estrogens in inflammation. Endocr Rev 2007;28:521-74.

22. Hall OJ, Klein SL. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. Mucosal Immunol 2017;10:1097-107.

23. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr 2021;180:2019-34.

24. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-7.

25. Santos MO, Gonçalves LC, Silva PAN, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J) 2022;98:338-49.

26. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol 2021;56:837-48.

27. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021;325:1074-87.

28. Dufort EM, Koumans EH, Chow EJ, et al. multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.

29. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323:2427-9.

30. Zhao Y, Yin L, Patel J, Tang L, Huang Y. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: a meta-analysis. J Med Virol 2021;93:4358-69.

31. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of us children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr 2021;175:837-45.

32. Stierman B, Abrams JY, Godfred-Cato SE, et al. Racial and ethnic disparities in multisystem inflammatory syndrome in children in the United States, March 2020 to February 2021. Pediatr Infect Dis J 2021;40:e400-6.

33. Rafferty MS, Burrows H, Joseph JP, Leveille J, Nihtianova S, Amirian ES. Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: current knowledge and implications for public health. J Infect Public Health 2021;14:484-94.

34. Javalkar K, Robson VK, Gaffney L, et al. Socioeconomic and racial and/or ethnic disparities in multisystem inflammatory syndrome. Pediatrics 2021;147:e2020039933.

35. Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 2021;4:e2116420.

36. Tyris J, Boggs K, Bost J, et al. Examining the association between MIS-C and the child opportunity index at a single center. Hosp Pediatr 2022;12:e342-8.

37. Dennis-Heyward EA. Disparities in susceptibility to multisystem inflammatory syndrome in children. JAMA Pediatr 2021;175:892-3.

38. Lee PY, Platt CD, Weeks S, et al. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. J Allergy Clin Immunol 2020;146:1194-1200.e1191.

39. Chou J, Platt CD, Habiballah S, et al. Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol 2021;148:732-738.e731.

40. Abuhammour W, Yavuz L, Jain R, et al. Genetic and clinical characteristics of patients in the middle east with multisystem inflammatory syndrome in children. JAMA Netw Open 2022;5:e2214985.

41. Vagrecha A, Zhang M, Acharya S, et al. Hemophagocytic lymphohistiocytosis gene variants in multisystem inflammatory syndrome in children. Biology (Basel) 2022;11:417.

42. Porritt RA, Paschold L, Rivas MN, et al. HLA class I-associated expansion of TRBV11-2 T cells in multisystem inflammatory syndrome in children. J Clin Invest 2021;131:e146614.

43. Sacco K, Castagnoli R, Vakkilainen S, et al. Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19. Nat Med 2022;28:1050-62.

44. Alsaied T, Tremoulet AH, Burns JC, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 2021;143:78-88.

45. Sharma C, Ganigara M, Galeotti C, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol 2021;17:731-48.

46. McMurray JC, May JW, Cunningham MW, Jones OY. Multisystem inflammatory syndrome in children (MIS-C), a post-viral myocarditis and systemic vasculitis: a critical review of its pathogenesis and treatment. Front Pediatr 2020;8:626182.

47. Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health 2020;4:790-4.

48. Duarte-Neto AN, Caldini EG, Gomes-Gouvêa MS, et al. An autopsy study of the spectrum of severe COVID-19 in children: from SARS to different phenotypes of MIS-C. EClnical Medicine 2021;35:100850.

49. Aeschlimann FA, Misra N, Hussein T, et al. Myocardial involvement in children with post-COVID multisystem inflammatory syndrome: a cardiovascular magnetic resonance based multicenter international study-the CARDOVID registry. J Cardiovasc Magn Reson 2021;23:140.

50. Dove ML, Oster ME, Hashemi S, Slesnick TC. Cardiac magnetic resonance findings after multisystem inflammatory syndrome in children. J Pediatr 2022;245:95-101.

51. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel, Switzerland) 2020;7:69.

52. Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med 2020;26:1701-7.

53. Vella LA, Rowley AH. Current insights into the pathophysiology of multisystem inflammatory syndrome in children. Curr Pediatr Rep 2021:1-10.

54. Moreews M, Le Gouge K, Khaldi-Plassart S, et al. Polyclonal expansion of TCR Vbeta 21.3(+) CD4(+) and CD8(+) T cells is a hallmark of multisystem inflammatory syndrome in children. Sci Immunol 2021;6:eabh1516.

55. Gurlevik SL, Ozsurekci Y, Sağ E, et al. The difference of the inflammatory milieu in MIS-C and severe COVID-19. Pediatr Res 2022:1-10.

56. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020;183:982-995.e914.

57. Hoste L, Roels L, Naesens L, et al. TIM3+ TRBV11-2 T cells and IFNγ signature in patrolling monocytes and CD16+ NK cells delineate MIS-C. J Exp Med 2022:219.

58. Caldarale F, Giacomelli M, Garrafa E, et al. Plasmacytoid dendritic cells depletion and elevation of IFN-γ dependent chemokines CXCL9 and CXCL10 in children with multisystem inflammatory syndrome. Front Immunol 2021;12:654587.

59. Diorio C, Shraim R, Vella LA, et al. Proteomic profiling of MIS-C patients indicates heterogeneity relating to interferon gamma dysregulation and vascular endothelial dysfunction. Nat Commun 2021;12:7222.

60. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest 2020;130:5967-75.

61. McCafferty C, Cai T, Borgel D, et al. Pathophysiological pathway differences in children who present with COVID-19 ARDS compared to COVID-19 induced MIS-C. Nat Commun 2022;13:2391.

62. Vella LA, Giles JR, Baxter AE, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Sci Immunol 2021:6.

63. Cheng MH, Zhang S, Porritt RA, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci USA 2020;117:25254-62.

64. Ramaswamy A, Brodsky NN, Sumida TS, et al. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. Immunity 2021;54:1083-1095.e1087.

65. Beckmann ND, Comella PH, Cheng E, et al. Downregulation of exhausted cytotoxic T cells in gene expression networks of multisystem inflammatory syndrome in children. Nat Commun 2021;12:4854.

66. Wu EY, Campbell MJ. Cardiac manifestations of multisystem inflammatory syndrome in children (MIS-C) following COVID-19. Curr Cardiol Rep 2021;23:168.

67. Porritt RA, Binek A, Paschold L, et al. The autoimmune signature of hyperinflammatory multisystem inflammatory syndrome in children. J Clin Invest 2021;131:e151520.

68. Pfeifer J, Thurner B, Kessel C, et al. Autoantibodies against interleukin-1 receptor antagonist in multisystem inflammatory syndrome in children: a multicentre, retrospective, cohort study. Lancet Rheumatol 2022;4:e329-37.

69. Levy M, Recher M, Hubert H, et al. Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. JAMA 2022;327:281-3.

70. Zambrano LD, Newhams MM, Olson SM, et al. BNT162b2 mRNA vaccination against covid-19 is associated with decreased likelihood of multisystem inflammatory syndrome in US children ages 5-18 years. Clin Infect Dis 2023;76:e90-100.

71. Nygaard U, Holm M, Hartling UB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. Lancet Child Adolesc Health 2022;6:459-65.

72. Truong DT, Dionne A, Muniz JC, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults: suspected myocarditis after COVID-19 vaccination. Circulation 2022;145:345-56.

73. Ouldali N, Bagheri H, Salvo F, et al. Hyper inflammatory syndrome following COVID-19 mRNA vaccine in children: a national post-authorization pharmacovigilance study. Lancet Reg Health Eur 2022;17:100393.

74. Yousaf AR, Cortese MM, Taylor AW, et al. Reported cases of multisystem inflammatory syndrome in children aged 12-20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation. Lancet Child Adolesc Health 2022;6:303-12.

75. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005;191:499-502.

76. McCrindle BW, Manlhiot C. SARS-CoV-2-related inflammatory multisystem syndrome in children: different or shared etiology and pathophysiology as Kawasaki Disease? JAMA 2020;324:246-8.

77. Bukulmez H. Current understanding of multisystem inflammatory syndrome (mis-c) following COVID-19 and its distinction from Kawasaki disease. Curr Rheumatol Rep 2021;23:58.

78. Kang JM, Kim YE, Huh K, et al. Reduction in Kawasaki disease after nonpharmaceutical interventions in the COVID-19 era: a nationwide observational study in Korea. Circulation 2021;143:2508-10.

79. Burney JA, Roberts SC, DeHaan LL, et al. Epidemiological and clinical features of Kawasaki disease during the COVID-19 pandemic in the United States. JAMA Netw Open 2022;5:e2217436.

80. Kim BJ, Choi A, Kim HS, et al. Changes in the clinical characteristics of Kawasaki disease after coronavirus disease (COVID-19) pandemic: a database analysis. J Korean Med Sci 2022;37:e141.

81. Roh DE, Lim YT, Kwon JE, Kim YH. Kawasaki disease following SARS-CoV-2 infection: stronger inflammation with no increase in cardiac complications. Front Pediatr 2022;10:1036306.

82. Beckley M, Olson AK, Portman MA. Tolerability of COVID-19 infection and messenger RNA vaccination among patients with a history of Kawasaki disease. JAMA Netw Open 2022;5:e2226236.

83. Sancho-Shimizu V, Brodin P, Cobat A, et al. SARS-CoV-2-related MIS-C: a key to the viral and genetic causes of Kawasaki disease? J Exp Med 2021;218:e20210446.

84. Rodriguez-Smith JJ, Verweyen EL, Clay GM, et al. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. Lancet Rheumatol 2021;3:e574-84.

85. Ghosh P, Katkar GD, Shimizu C, et al. An artificial intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. Nat Commun 2022;13:2687.