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Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison

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Abstract

Children and adolescents infected with SARS-CoV-2 are predominantly asymptomatic or have mild symptoms compared with the more severe COVID-19 described in adults. However, SARS-CoV-2 is also associated with a widely reported but poorly understood paediatric systemic vasculitis. This multisystem inflammatory syndrome in children (MIS-C) has features that overlap with myocarditis, toxic-shock syndrome and Kawasaki disease. Current evidence indicates that MIS-C is the result of an exaggerated innate and adaptive immune response, characterized by a cytokine storm, and that it is triggered by prior SARS-CoV-2 exposure. Epidemiological, clinical and immunological differences classify MIS-C as being distinct from Kawasaki disease. Differences include the age range, geographic and ethnic distribution of patients. MIS-C is associated with prominent gastrointestinal and cardiovascular system involvement, intensive-care-unit admission, neutrophilia, lymphopenia, high levels of IFN γ and low counts of naïve CD4⁺ T cells, with a high proportion of activated memory T cells. Further investigation of MIS-C will continue to enhance our understanding of similar conditions associated with a cytokine storm.

[H1]Introduction

Our understanding of the coronavirus disease-2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has improved greatly since the first human cases were reported in December 2019 in Wuhan City, China^{1,2}. COVID-19 is known to involve multiple organ systems, with the major disease burden resulting from respiratory, cardiovascular, thrombotic and neurological complications³⁻⁵. Cellular entry of SARS-CoV-2 depends on binding of the viral spike (S) protein to cellular receptors, such as angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in multiple organ

systems^{6,7}, and on S-protein priming by host-cell proteases^{8,9}. In some individuals these steps are followed by a cascade of inflammatory events, resulting in a ‘cytokine storm’⁷. This massive pro-inflammatory cellular and cytokine response is a feature of patients with severe COVID-19 disease¹⁰.

Although morbidity and mortality from primary COVID-19 infection have remained limited in children, we have witnessed the emergence of a new inflammatory disorder associated with COVID-19, termed multisystem inflammatory syndrome in children (MIS-C) in the USA and paediatric inflammatory multisystemic syndrome (PIMS) in Europe^{11–15}. Current evidence suggests that MIS-C is a post-infectious, immunologically-mediated disorder related to prior SARS-CoV-2 exposure or infection^{16–18}. Epidemiological, clinical and immunological investigations have revealed that MIS-C has phenotypic similarities to Kawasaki disease, a childhood inflammatory vasculitis, and it has been suggested that SARS-CoV-2 acts as an additional infectious trigger of Kawasaki disease, leading to an exaggerated phenotype along the same disease spectrum. However, in this Review we present evidence that although MIS-C has some features that overlap with Kawasaki disease, they are distinct syndromes that differ in degrees of hyperinflammation and dysregulated immune responses (**Table 1**).

[H1] Overview of Kawasaki disease

Kawasaki disease is a paediatric, self-limited, systemic inflammatory vasculitis that was first described in 1967 in Japan by Dr Tomisaku Kawasaki¹⁹. The most important long-term sequelae of Kawasaki disease relate to abnormalities of the coronary artery, and it is now the most common cause of acquired heart disease in children in the developed world²⁰. A diagnostic feature of Kawasaki disease is fever that persists for more than 5 days when untreated. Additional typical clinical features include polymorphic skin rash (erythema), involvement of lips and oral mucosa (lip fissures, strawberry tongue), lymphadenopathy (cervical, often unilateral), non-exudative bilateral conjunctivitis and extremity changes (erythema and oedema of palms and soles that desquamate after 2–3 weeks, usually seen in the subacute phase)²⁰.

[H2] Aetiology

The aetiology of Kawasaki disease is uncertain, and there is no single specific diagnostic test. The general consensus, based on results from multiple studies, is that Kawasaki disease is an

immune-mediated disease triggered by infection(s) in patients with a genetic predisposition^{21–25}. Some epidemiological features offer clues to the pathogenesis of Kawasaki disease. It is typically noted in children between the ages of 6 months and 5 years, with an estimated incidence of 25 cases per 100,000 children <5-years old in North America^{20,26}. It is believed that children <6-months old, who have immature immune systems, are protected by passive immunity provided by the transplacental transfer of maternal antibodies, whereas children >5-years old have developed protective antibody responses to the ubiquitous antigens that most encounter uneventfully in early childhood²⁷. There is a male predominance (~1.5:1) in the incidence of Kawasaki disease, a feature that is shared by many common childhood infectious diseases^{28,29}.

Seasonal variation in the incidence of Kawasaki disease has been noted, with peak incidence occurring in winter and spring in the USA and UK, and in summer in China and Korea^{30–34}. Seasonal variation is least evident in Japan, the country with the highest incidence of Kawasaki disease^{35,36}. Geographical variation and clustering in the incidence of Kawasaki disease also occurs, with the highest incidence reported in Japan, China, South Korea and Taiwan^{35,37–39}. These epidemiological features point towards a transmissible infectious agent, which tends to occur in certain regions of the world with a seasonal variation in its incidence. Evidence exists for the presence of concurrent infections (with bacteria or common respiratory viruses, including coronaviruses) in patients with Kawasaki disease^{40–42}. Immunohistochemistry analyses have shown infiltration of IgA plasma cells indicative of the antigen-driven immune response in inflamed tissues, and the presence of cytoplasmic antigens suggestive of an infectious aetiology in bronchial and vascular endothelial cells and macrophages⁴³. However, to date no single organism has been directly proven to cause Kawasaki disease^{44,45}.

[H2]Involvement of superantigens

The potential pathogenic role of superantigens has been evaluated, on the basis of observations of preferential expression of T-cell receptor (TCR) β genes encoding variable regions V β 2 and V β 8.1 in the peripheral-blood lymphocytes of patients with acute Kawasaki disease^{46–48}. Superantigen activity has been identified in the gut microbiota of such patients, and culture supernatants of these bacteria contain a heat-shock protein (Hsp60, also known as GroEL) that induces T-cell division and production of pro-inflammatory cytokines⁴⁹. However, in studies using flow cytometry in large series of patients with Kawasaki disease, TCR skewing and over-

presentation of the described TCR clones has not been found, and it is currently believed that Kawasaki disease is a result of T-cell activation by a conventional antigen^{50,51}.

[H2]Involvement of nutritional disorders

The role of nutritional disorders, including vitamin D deficiency, in the pathogenesis of Kawasaki disease is subject to debate⁵². Vitamin D has an anti-inflammatory effect mediated through elevation of expression of IL-10 and inhibition of that of vascular endothelial growth factor^{53,54}. Results from a German population-based study showed that vitamin D supplementation has a protective effect against the development of Kawasaki disease⁵⁵. Low serum concentrations of vitamin D might contribute to the development of coronary artery complications in children with Kawasaki disease⁵⁶. However, other results have identified elevation of vitamin D levels during the acute phase of Kawasaki disease in children who subsequently developed coronary arterial lesions⁵⁷. The contribution of other nutritional factors has also been suggested. For example, iron-deficiency anaemia is associated with development of coronary abnormalities in Kawasaki disease⁵⁸. These varied results suggest the need for further investigation and research to elucidate the role of malnutrition in the pathogenesis of Kawasaki disease.

[H2]The role of microbiota

Disturbances in the normal microbiota (dysbiosis) have been proposed to have a role in the pathogenesis of various autoimmune and inflammatory disorders, including Kawasaki disease^{59–61}. Stools from children with Kawasaki disease contain higher numbers of Gram-positive bacteria from the *Streptococcus*, *Staphylococcus*, *Eubacterium* and *Peptostreptococcus* genera, as well as Hsp60-producing Gram-negative bacteria, and lower numbers of Lactobacilli than stools from children with other febrile illnesses or healthy controls^{49,61,62}. Dysbiosis is associated with reduction of the production of short-chain fatty acids (particularly butyrate), and is proposed to lead to aberrant immune responses that are associated with Kawasaki disease⁶³.

[H2]Genetic susceptibility

Epidemiological and genetic studies of Kawasaki disease have shed light on the role of genetic susceptibility in its development⁶⁴. Kawasaki disease is prevalent in Japan, but also in children of

Japanese ancestry living in Hawaii⁶⁵. Siblings of children with Kawasaki disease have a 10-fold higher risk of development of the condition than children in the general population⁶⁶. Several candidate genes have been identified through genome-wide association studies and linkage studies. The four major groups of genes that have been studied in Kawasaki disease are those associated with T-cell activation (*ORAI1* and *STIM1*), B-cell signalling (*CD40*, *BLK* and *FCGR2A*), apoptosis (*CASP3*) and transforming growth factor β (TGF β) signalling (*TGFB2*, *TGFBR2*, *MMP* and *SMAD*)⁶⁴. *CASP3* encodes caspase-3, which is an effector caspase with a vital role in the execution phase of apoptosis. A single-nucleotide polymorphism in the *CASP3* gene is associated with susceptibility to Kawasaki disease⁶⁷. TGF β is another vital protein with a central role in immunoregulation affecting multiple populations of leukocytes. Abnormalities in TGF β signalling resulting from genetic variation are involved in Kawasaki disease susceptibility and outcomes⁶⁸. Understanding the roles of these genetic alterations has implications for potential therapeutic approaches⁶⁹. In addition to these groups, mutations in *ITPKC*, which is involved in Ca²⁺ mobilization and activation of NLRP3 inflammasomes, could result in enhancement of IL-1 β and IL-18 production, disease susceptibility, coronary abnormalities and resistance to treatment with intravenous immunoglobulin (IVIG)^{70,71}. Notably, immunosuppressive agents such as ciclosporin, a T-cell inhibitor that blocks the calcineurin-NFAT pathway, have shown promise in the treatment of high-risk IVIG-resistant Kawasaki disease⁷². The observed association of HLA polymorphisms with Kawasaki disease varies; the predominant variant in a Japanese cohort was HLA-Bw54, whereas HLA-Bw51 was predominantly identified in white and Jewish populations⁷³⁻⁷⁵. Epigenetic regulation of inflammatory and immunoregulatory genes by factors such as methylation, micro-RNAs and long non-coding RNAs has been identified in Kawasaki disease, and might be relevant to pathogenesis and prognosis⁷⁶. Additionally, single-nucleotide polymorphisms in cytokine genes, including *IL-1*, *KCNN2*, *TIFAB*, *P2RY12* and *TNF*, are associated with Kawasaki disease and with risk of coronary artery lesions, as well as IVIG treatment failure⁷⁷⁻⁸².

[H2]Immunological aberrations

Innate and adaptive immune responses both have important roles in the development of Kawasaki disease⁸³. An intense initial response driven by the innate immune system takes the form of neutrophilic leukocytosis, activation of monocytes, natural killer (NK) cells and $\gamma\delta$ T

cells, and elevation of production of acute-phase reactants and cytokines, especially IL-1 β , which contributes to activation of endothelial cells, inducing upregulation of expression of cell-adhesion molecules, *IL6* and *IL8*⁷⁶⁻⁸⁸. Pro-inflammatory IL-17 produced by type 17 T helper (T_H17) cells could activate immune cells such as neutrophils and monocytes, leading to production of other inflammatory cytokines, such as IL-6, TNF and IL-8, thereby contributing to the pathogenesis of many inflammatory disorders⁸⁹⁻⁹². By contrast, CD4⁺CD25⁺ regulatory T (T_{reg}) cells contribute to immune tolerance through suppression of the hyperactivation of both innate and adaptive immune cells, via several mutually nonexclusive mechanisms. An imbalance in these pathways could lead to immune dysregulation, which could have a role in the pathogenesis of Kawasaki disease⁹³⁻⁹⁶.

Neutrophils are activated in Kawasaki disease and release reactive oxygen species, leading to endothelial cell injury⁸³. Release of neutrophil extracellular traps (NETs) is also implicated in the pathogenesis of Kawasaki disease⁹⁷. Although NETs have a protective role against infections as components of the innate immune system, they also have pathogenic potential for immune dysregulation and promotion of inflammation and tissue injury⁹⁸. NETs have been implicated in the development and progression of rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis and autoimmune vasculitis⁹⁹⁻¹⁰¹. Yoshida et al. demonstrated elevation of NET formation in the sera of patients with Kawasaki disease, as well as neutrophil infiltration in the lesions of vasculitis in the coronary arteries and aorta in a mouse model of Kawasaki disease⁹⁷.

Autoimmune antibodies are thought to have a role in the pathogenesis of Kawasaki disease, particularly those against endothelial-cell antigens^{102,103}. Anti-endothelial-cell antibodies could cause endothelial damage, with release of pro-inflammatory cytokines and a hypercoagulable state leading to vessel-wall injury and intravascular thrombosis¹⁰⁴. However, not all results have demonstrated elevation of anti-endothelial-cell antibodies in patients with Kawasaki disease¹⁰⁵.

Immune complexes might have a role in the development of Kawasaki disease¹⁰⁶. They appear in the first 7 days of the disease and peak in the second week before declining¹⁰⁷. Elevation of circulating levels of immune complexes in Kawasaki disease is related to adverse outcomes such as coronary artery abnormalities^{108,109}. However, a causal relationship between immune complexes and the pathogenesis of Kawasaki disease has not been definitively

established. Activation of the complement system has also been implicated in the pathogenesis of Kawasaki disease, both via the classical and the mannose-binding lectin pathways^{110,111}.

Kawasaki disease is considered by some to be a form of IgA vasculitis. In children with Kawasaki disease, intestinal permeability and levels of secretory IgA in the circulation are greater than in unaffected children, and in mouse models of the disease, elevation of levels of circulating secretory IgA and IgA deposition in the vasculature are observed^{112,113}. Furthermore, pharmacological blockade of zonulin (a modulator of intestinal tight junctions) and administration of IVIG in these mouse models reduce intestinal permeability and cardiovascular inflammation compared with levels in untreated controls¹¹⁴.

[H2]Therapeutic strategies

IVIG and acetylsalicylic acid have emerged as first-line therapies for the management of Kawasaki disease¹¹⁵. IVIG therapy leads to rapid improvement in the clinical symptoms of rash, fever and conjunctival injection in the majority of patients. Although the exact mechanism of action of IVIG is not yet known, proposals include inhibition of activation of innate immune cells and inflammatory mediators, expansion of T_{reg} cells and suppression of T_H17 cells^{93,116–119}. Evidence indicates that IVIG might target IL-1 β ⁺ neutrophils via caspase-independent pathways¹²⁰. Single-cell RNA sequencing of peripheral blood mononuclear cells in acute Kawasaki disease before and after IVIG therapy has revealed that genes encoding inflammatory mediators (including *TNF* and *IL1B*) are highly expressed in monocytes in untreated disease, with reduction of expression following therapy, along with significant enhancement of the plasma-cell population and induction of oligoclonal expansion of T-cell receptors and IgG and IgA B-cell receptors¹²¹. Mining of transcriptomic data by Boolean analysis has identified that several metabolic pathways might contribute to IVIG resistance in Kawasaki disease¹²². In high-risk patients with acute Kawasaki disease and in those who do not respond to IVIG therapy, steroid treatment can be considered, to prevent the occurrence of coronary artery abnormalities²⁰. Additional therapeutic options for IVIG-resistant Kawasaki disease include infliximab (a monoclonal antibody to TNF), ciclosporin (a calcineurin inhibitor) and anakinra (an IL-1 receptor antagonist)²⁰.

[H1]Overview of MIS-C

Since April 2020, many reports have documented a new hyper-inflammatory syndrome in children^{11,12,123}. In May 2020, the US Centers for Disease Control and Prevention (CDC) issued an alert identifying MIS-C as a critical illness in children that was associated with SARS-CoV-2 infection¹²⁴. Since then, >4,000 cases of MIS-C have been reported in the USA alone¹²⁵. In 26 studies published in 2020 and 2021, documenting a total of 1,136 cases of MIS-C (mostly occurring in the USA and Europe), the reported median ages of the affected children were 6–11 years, with no significant gender difference (**Table 2**)^{14,15,123,126–141}.

Patients with MIS-C have symptoms that resemble those of other hyper-inflammatory syndromes, such as Kawasaki disease, toxic-shock syndrome (TSS) and macrophage activation syndrome (MAS), which is a type of secondary haemophagocytic lymphohistiocytosis^{11,12}. To improve clarity and aid diagnosis, the CDC published a case definition, which includes age <21 years, fever, laboratory evidence of inflammation, hospital admission, multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological or neurological), either laboratory confirmation of SARS-CoV-2 infection (by RT-PCR, serology or antigen test) or known COVID-19 exposure up to 4 weeks prior to symptom onset, with no alternative plausible diagnosis¹²⁴. The WHO and the UK Royal College of Paediatrics and Child Health (RCPCH) have also published case definitions, which are largely similar to the CDC definition, except that the RCPCH does not require evidence of prior exposure to SARS-CoV-2^{142,143}. Despite the broad case definitions, and the considerable overlap with primary COVID-19 and other common childhood febrile illnesses, patients with MIS-C have distinct clinical presentation and levels of biomarkers, which aids in differential diagnosis^{144–146}.

[H2]Aetiology

Compared with adults, primary SARS-CoV-2 infection is relatively mild in children¹⁴⁷. Evidence indicates that a temporal relationship exists between SARS-CoV-2 exposure and development of MIS-C, as a spike in MIS-C cases occurs 3–6 weeks after the peak of SARS-CoV-2 transmission in a community (FIG. 1)^{13,130,148}. Median intervals of 21 and 25 days have been observed between the occurrence of COVID-19 symptoms and the onset of MIS-C^{13,14}. Whereas 80–90% of MIS-C patients have been found to be SARS-CoV-2 seropositive, positivity in PCR testing is only 20–40%, suggesting that the interval to the onset of MIS-C is sufficient for viral RNA levels to fall considerably^{149,150}. Furthermore, nasopharyngeal aspirates from patients with MIS-

C have higher SARS-CoV-2 real-time RT-PCR cycle thresholds (indicating lower levels of viral RNA) than those from patients with severe COVID-19¹⁵¹. However, autopsy examinations for three individuals who had MIS-C identified SARS-CoV-2 in various tissues, including heart, kidneys, brain and intestine, which is consistent with multisystem organ involvement in MIS-C¹⁵². Notably, the prolonged presence of SARS-CoV-2 in children's intestines might cause zonulin-dependent loss of tight junctions, leading to leakage of viral antigens into the circulation, and to hyperinflammation and MIS-C¹⁵³. By contrast, single-cell RNA sequencing of peripheral-blood mononuclear cells from patients with acute MIS-C have revealed low viral and bacterial signatures in the immune cells, suggesting that active viral or bacterial infectious triggers are not contributing factors¹⁵⁴. The accumulated evidence suggests that MIS-C might be the result of a combination of post-infectious immune dysregulation and virus-induced cytopathic effects and inflammation in multiple organ systems.

Paediatric patients with COVID-19 or MIS-C have strong IgG, but weak IgM antibody responses to the trimeric S glycoprotein of SARS-CoV-2, and weak responses to the nucleocapsid protein N, which is implicated in viral replication^{141,155–159}. By contrast, adult COVID-19 patients had higher levels of anti-S antibodies, broader immunoglobulin response to SARS-CoV-2 with respect to specificity and isotype distribution (including IgG, IgM and IgA isotypes), and higher virus-neutralizing capacity^{141,156,157,159}. The mild or asymptomatic nature of COVID-19 in children might be related to the extent of the antibody response. Nevertheless, IgG antibodies to S protein provide an important diagnostic criterion for MIS-C. Low IgM titres in MIS-C are consistent with its appearance several weeks after SARS-CoV-2 exposure.

Analyses from geographically diverse cohorts have demonstrated that 20–50% of people with no previous exposure to the virus have T-cell reactivity against peptides corresponding to SARS-CoV-2 sequences¹⁶⁰, which might be related to CD4⁺ T-cell cross-reactivity with circulating seasonal human 'common cold' coronavirus (HCoV)¹⁶¹. Although this phenomenon has implications for the development of herd-immunity models and vaccine candidates, it is currently unclear whether the presence of prior cross-reactive CD4⁺ T cells is protective or harmful in the pathogenesis of MIS-C. When tested for serological evidence of prior seasonal coronavirus infection, children with MIS-C and those hospitalized for non-COVID reasons had similar prevalence and levels of antibodies to HCoV¹⁶². Additionally, HCoV antibody levels did not correlate with the levels of SARS-CoV-2 antibodies, suggesting that prior HCoV infection

neither provides protection nor worsens the course of paediatric SARS-CoV-2 infection or MIS-C.

[H2]SARS-CoV-2 S protein as a superantigen

SARS-CoV-2 viral S-protein might behave like a superantigen, triggering a cytokine storm that results in the development of the TSS-like presentation of MIS-C (FIG. 2)¹⁶³. The S protein has a high-affinity motif for binding TCR, which is similar in structure to the staphylococcal enterotoxin B, a superantigen that mediates TSS by interacting with both TCR and MHC class II molecules. Computational modelling has shown that SARS-CoV-2 encodes a superantigen motif near the S1/S2 cleavage site, which interacts with both the TCR and CD28¹⁶⁴. TCR repertoire analysis of T cells in a small number of patients with MIS-C has identified skewing of TCR V β towards TRBV11-2 (V β 21.3), which is associated with HLA Class I alleles A02, B35 and C04^{164,165}. The CDR3-independent nature of TCR V β skewing suggested superantigen-mediated activation of T cells in MIS-C. Further evidence supports the enrichment of TRBV11-2 among T cells^{154,166}, although notably it has been observed in the absence of differential expression of a set of ‘superantigen genes’¹⁵⁴. Also, MIS-C is usually observed several weeks after primary SARS-CoV-2 exposure, in contrast to the acute illness and cytokine storm observed in TSS¹⁶⁷. In most cases, SARS-CoV-2 is undetectable in patients with MIS-C during acute phase of inflammation. Thus, the superantigenic property of SARS-CoV-2 S protein and its implication in MIS-C is not yet confirmed. As an RNA virus, SARS-CoV-2 undergoes constant mutation, and whether any particular variant of the virus contributes to MIS-C by triggering strong inflammatory signalling in the immune cells and endothelial cells of children with COVID-19 requires further exploration. Notably, the use of *in silico* techniques has demonstrated that mutations in the binding region of SARS-CoV-2 S protein could influence the interaction with MHC class II molecules and TCR¹⁶⁴.

[H2]Involvement of nutritional disorders

Nutritional factors such as vitamin D deficiency might have a role in the development of MIS-C. Adults with vitamin D deficiency were noted to have a more severe form of COVID-19 with an increased risk of death than those without this deficiency¹⁶⁸. Vitamin D supplementation has

proved to be of some benefit in infections with other viruses, such as influenza A¹⁶⁹. Whether a similar benefit could accrue in MIS-C has not been elucidated.

[H2]The role of microbiota

Another contributing factor in the development of MIS-C that warrants investigation is the role of gut and respiratory tract microbiota. Gastrointestinal microbes are important regulators of the gut immune system and inflammation, and influence the balance between T_H17 cells and T_{reg} cells¹⁷⁰. Adult patients with COVID-19 display alteration of gut and upper respiratory microbiomes, and gut dysbiosis persists beyond the nasal clearance of SARS-CoV-2^{171–174}. Notably, faecal SARS-CoV-2 load is inversely correlated with the abundance of bacteria of the Bacteroidetes phylum, which suppress ACE2 in the mouse gut¹⁷⁴. Preliminary data from peer-reviewed and non-peer reviewed reports also suggest the persistence of microbiome dysbiosis in the upper respiratory tract and the gut in paediatric COVID-19^{175,176}.

[H2]Genetic susceptibility

The low incidence of MIS-C relative to COVID-19, and the similarity in antibody response to SARS-CoV-2 in paediatric patients with MIS-C and with COVID-19 (irrespective of the subsequent development of MIS-C) suggest that SARS-CoV-2 infection causes dysregulation of immune responses in a subgroup of predisposed children with particular genetic backgrounds¹⁷⁷. Specifically, predisposition might be related to mutations and polymorphisms in the genes that encode pattern-recognition molecules like toll-like receptors, components of the signalling cascades of the immune response, and Fcγ receptors (FIG. 2). The incidence of MIS-C is higher in children of African and Hispanic heritage than in those of other ethnicities, although attribution of this finding to genetic differences is confounded by the contribution of socioeconomic factors to the risks of SARS-CoV-2 infection^{178–181}. Among 145 HLA-A, HLA-B and HLA-C genotypes, *HLA-B*46:01* was associated with *in silico* prediction of the fewest SARS-CoV-2 binding peptides (suggesting particular vulnerability to COVID-19), whereas *HLA-B*15:03* was predicted to have the greatest capacity for coronavirus peptide presentation (suggesting protective T cell-based immunity)¹⁸². Monogenic loss-of-function variants affecting immunity in the type I IFN signalling pathway might confer a predisposition to severe COVID-19 manifestations^{183,184}. In a study of two unrelated patients with infection-associated immune

thrombocytopenia and autoimmune haemolytic anaemia, both had *SOCS1* haploinsufficiency and exhibited T-cell activation and high levels of IFN signalling, and one developed MIS-C after SARS-CoV-2 infection. SOCS are negative regulators of IFN signalling, and silencing mutations might predispose the individuals to infection-associated hyperinflammatory states such as MIS-C (FIG. 2)¹⁸⁵. However, a clear genetic basis that explains why some children develop MIS-C after SARS-CoV-2 exposure is currently undetermined. Additional factors, such as epigenetic effects at the level of histones, DNA or microRNA might also contribute to the development of MIS-C.

[H2]Immunological aberrations

In general, the signatures of immune cells and inflammatory parameters of MIS-C closely overlap with those of adults with moderate-to-severe COVID-19 rather than with paediatric COVID-19, which is mostly mild or asymptomatic. Also, immune activation in MIS-C is transient and tends to reduce during recovery^{155,186,187}.

[H3]Pro-inflammatory mediators

Elevation of levels of pro-inflammatory cytokines such as IL-6, IL-10 and IL-17A, and chemokines such as CXCL5, CXCL11, CXCL1 and CXCL6 in MIS-C distinguishes it from paediatric COVID-19^{137,154,155,188}. In various cohorts, elevation of TNF, IL-1 β , IFN γ , soluble IL-2R, CCL2, CCL3, CCL4, CXCL8 (IL-8) or IFN γ -induced chemokines CXCL9 and CXCL10 has been reported in the serum of patients with MIS-C relative to those with paediatric COVID-19 or healthy controls^{137,154,151,166,187-190}. Overall, enhancement of these pro-inflammatory molecules in the circulation indicates inflammatory responses of myeloid and lymphoid cells. Endothelial cells could also contribute innate inflammatory mediators, as E-selectin, a marker of inflamed endothelial cells, shows elevation in the serum of patients with MIS-C¹⁵⁴. The reasons for the absence of some pro-inflammatory mediators in particular cohorts of patients are not known. The mediators that were analysed could have differed from study to study, but also, the levels of inflammatory mediators might vary depending on the patients' genetic and epigenetic backgrounds, severity of the disease, geographical locations and timing of the analyses. Results from a study of plasma proteomics in children with SARS-CoV-2 infection, which have not yet undergone peer review, suggest that IFN γ expression is heterogeneous among patients with MIS-C, and that IFN γ levels might be inversely associated with MIS-C severity¹⁹¹. As the pandemic progresses, it will be important to have a consensus regarding the panel of cytokines and

chemokines that should be analysed in relation to MIS-C, to facilitate our understanding of the molecular pathogenesis and heterogeneity of this complex disease, and to enable accurate prognosis and effective treatment.

[H3]Immune-cell profiles

Immune-cell profiling of children with MIS-C or primary COVID-19 infection reveals similarities as well as differences in their immune signatures¹⁸⁶. They have similar proportions of eosinophils, immature granulocytes, monocytes and classic dendritic cells, but patients with MIS-C have elevation of neutrophils and reduction of plasmacytoid dendritic cells^{154,186,189}, which might contribute to the low levels of IFN α that are observed in the blood of patients with MIS-C relative to those with paediatric COVID-19¹⁸⁹.

Neutrophils and monocytes are activated in patients with MIS-C¹⁸⁷, and show upregulation of alarmin signatures (in particular *S100A* genes) and reduction of expression of antigen-presenting, antigen-processing and co-stimulatory molecules^{154,166,187}. Compared with healthy children, those with MIS-C have greater expression of cytotoxicity genes and *CCL4* in NK cells, which might contribute to the occurrence of tissue damage¹⁵⁴. Preliminary results suggest that plasma levels of IFN γ significantly correlate with levels of NCR1 and IL2RA, which are the soluble markers of activated NK and T cells, respectively¹⁹¹.

MIS-C could have a common pathophysiology with Kawasaki disease involving NET formation, which has been described in the sera of adults with COVID-19 and with endothelial injuries or a prothrombotic state^{192–194}. However, plasma levels of NETs and release of NETs from neutrophils are similar in children with mild or moderate COVID-19 or MIS-C and in healthy children¹⁹⁵. Despite similarities between disorders associated with pathogenic NETs and MIS-C, the role of NETosis in the pathogenesis of MIS-C remains uncertain because of a lack of definitive evidence, and hence further studies are warranted.

Both MIS-C and paediatric COVID-19 present with general lymphopenia (affecting cells including mucosal-associated invariant T cells, $\gamma\delta$ T lymphocytes and CD8⁺ T lymphocytes)^{137,151,155,186–189}. Compared with paediatric COVID-19, in MIS-C there is more-pronounced CD4⁺ T-cell-biased lymphopenia, which is similar to the situation in severely ill adults with COVID-19¹⁸⁶. However, results from single-cell RNA-sequencing analysis have revealed enhanced proliferation of CD4⁺ T cells in patients with MIS-C compared with healthy individuals¹⁵⁴, suggesting that lymphopenia might be the result of homing of T cells to the

inflamed tissues. Despite showing T-cell lymphopenia, the relative distribution of various T-cell subsets like naïve, central memory and effector memory cells in patients with MIS-C is similar to that in age-matched healthy individuals, indicating a pan-CD4⁺/CD8⁺ T-cell lymphopenia, rather than a subset-specific effect^{155,186}.

A distinct feature of MIS-C compared with paediatric COVID-19 is the activation of CX3CR1⁺CD8⁺ T cells (CD8⁺ T cells that express vascular endothelium-homing CX3CR1, also known as fractalkine receptor), which could have implications for development of vascular abnormalities and cardiovascular abnormalities¹⁸⁶. This immunological phenotype is correlated with elevation of D-dimer, reduction of platelets, and with the requirement for vasoactive medication. Although not as prominent as in NK cells, CD8⁺ T cells in MIS-C also show increases in signatures of cytotoxicity compared with those in healthy children¹⁵⁴. RNA sequencing in blood from children with MIS-C revealed aberrant NK and CD8⁺ T-cell regulation, with depletion of NK cells and an absence of NK cell-dependent exhaustion of effector CD8⁺ T cells, which can lead to sustained inflammation¹⁹⁶. Notably, the proportion of activated CX3CR1⁺CD8⁺ T cells in patients with MIS-C decreases as the clinical status improves¹⁸⁶. Thus, there seems to be a sustained activation and dysregulation of CD8⁺ T cells, particularly those expressing CX3CR1.

Nonspecific activation of B-cell clones and expansion of plasmablasts occurs in MIS-C^{151,154,186,187}. Plasmablast elevation also occurs in children with COVID-19¹⁸⁶. However, the specificity of expanded B cells and plasmablasts might vary between the two conditions. Patients with MIS-C display pronounced autoreactivity signatures of plasma immunoglobulins compared with healthy children or adults and children with COVID-19^{154,155,103}. Also, patients with MIS-C have evidence of extrafollicular responses, as indicated by high frequencies of plasmablasts expressing the T-box transcription factor T-bet¹⁸⁶. Future research should aim to uncover the reasons for this B-cell activation, and should compare the characteristics of expanded B cells and plasmablasts, and the specificities of immunoglobulins, in MIS-C and paediatric COVID-19. As both conditions are associated with nonspecific B-cell activation and elevation of plasmablast frequencies¹⁹⁷, molecular mimicry between self-antigens and SARS-CoV-2 antigens (as described in a paper that has not yet been peer reviewed¹⁹⁸) might not be entirely responsible for the appearance of autoreactivity in MIS-C, and instead a combination of molecular mimicry and dysfunctional immunoregulatory machinery could be involved.

[H3]Humoral features

Analysis of IgG by systems serology has identified that humoral features in patients with MIS-C, such as complement deposition and neutrophil phagocytosis, overlap with those in convalescent adults with COVID-19¹⁵⁹. However, patients with severe MIS-C have persistent levels of Fc γ R binding (and in particular activating Fc γ RIIA) and inflammatory monocyte/macrophage-activating IgG¹⁵⁹. Although hypergammaglobulinaemia is not observed in patients with MIS-C, a selective expansion of the IgG repertoire to react not only to SARS-CoV-2, but also to other bacterial and viral pathogens, some which are implicated in the triggering of Kawasaki disease, has been observed. The underlying reason for the enrichment of particular IgG specificities is not yet known, but many of the microbes have been identified in the respiratory tracts of patients with MIS-C¹⁹⁹, suggesting a role for an immune-complex-driven inflammatory response in the pathogenesis of MIS-C. IgG and IgA autoantibodies occur in patients with MIS-C, and recognize gastrointestinal, mucosal, immune-cell and endothelial antigens^{154,155}. Although the functionality of these autoantibodies and their roles in the pathogenesis of MIS-C should be investigated, these results might explain at least in part the involvement of multiple organ systems in MIS-C, and provide a pointer towards bystander activation of B lymphocytes, enhanced autoreactivity and immune-complex-mediated inflammatory responses (FIG. 2). Enhanced expression of CD64 (Fc γ R1), a high-affinity receptor for the Fc fragment of IgG, has been observed on neutrophils and monocytes of patients with MIS-C^{155,187}. Furthermore, the majority of these patients respond to IVIG therapy^{11,15,123,130,132}, which provides additional indirect support for the implication of Fc γ R-mediated activation of innate immune cells by immune complexes formed by these IgGs.

A role for the complement system in the pathogenesis of MIS-C has been suggested. Patients with MIS-C or paediatric COVID-19 have elevated plasma levels of soluble C5b-9 compared with healthy controls^{151,200}. Soluble C5b-9 is a biomarker to monitor the activity of the terminal pathway of complement, and elevated levels suggest complement activation and endothelial dysfunction. Notably, although patients with MIS-C and paediatric COVID-19 have similar levels of complement-activating IgG antibodies to S protein of SARS-CoV-2^{141,155-159}, those with MIS-C have enhanced autoreactive signatures of IgG^{154,155,103}. As patients with MIS-C typically have minimal or no SARS-CoV-2 at the time of development of the disease, enhanced autoreactivity and immune-complex formation might contribute to the elevated levels

of C5b-9. Consistent with complement activation, MIS-C is associated with clinical criteria for complement-mediated thrombotic microangiopathy, such as microangiopathic haemolytic anaemia, hypertension, thrombocytopenia, proteinuria and evidence of organ damage on the basis of lactate dehydrogenase elevation²⁰⁰. Compared with paediatric COVID-19, patients with MIS-C have higher incidence of thrombotic events²⁰¹. Results from proteomics analyses of plasma samples, which have not yet been peer reviewed, suggest that phospholipase A2 (PLA2G2A) could be a biomarker for diagnosis of thrombotic microangiopathy in MIS-C¹⁹¹. The lectin complement pathway might also have an important role in the pathogenesis of diseases associated with SARS-CoV-2, as a result of the carbohydrate-residue-rich surface structures of the virus^{202–204}.

[H2]Therapeutic strategies

Treatment approaches to MIS-C aim to mute the exaggerated inflammatory response. Multiple approaches, borrowed from Kawasaki disease and other hyper-inflammatory syndromes, have been considered, ranging from IVIG to glucocorticoids and immunotherapy^{205,206}. MIS-C treatment regimens described in 24 studies, involving 1,020 individuals, are summarized in **Table 3**, highlighting the many variations on the theme of attempting to calm overactive inflammatory responses^{6,17,94,100–115,165}. In most studies, a majority (70–100%) of the patients were treated with IVIG as the first-line agent, with satisfactory results. Steroids were the second most common treatment employed for patients with MIS-C.

Shock and cardiovascular manifestations comprise a predominant mode of presentation of MIS-C, and high-dose glucocorticoids have been advocated for, and used successfully in, patients with shock. Widely followed guidance from the ACR recommends IVIG as first-line therapy in hospitalized patients with MIS-C, with addition of glucocorticoids in the presence of shock, organ-threatening disease or refractory disease¹⁵⁰. In a study of 181 children with suspected MIS-C, IVIG alone had a higher failure rate than the use of IVIG with methylprednisolone (OR 0.25; 95% CI 0.09–0.70)²⁰⁷. By contrast, results from a multinational observational cohort study involving 615 children with suspected MIS-C identified no difference in acute outcomes between primary treatment with IVIG alone, IVIG with steroids or steroids alone²⁰⁸. In view of the apparently important role of IL-1 β in the pathogenesis of MIS-C, anakinra (an IL-1 receptor antagonist) has been used in MIS-C that is refractory to therapy with

IVIg or steroids, extrapolating from its success in small groups of patients with IVIg-resistant Kawasaki disease^{123,149,209,210}.

Zonulin-dependent loss of intestinal mucosal permeability is implicated in mediation of the hyperinflammation observed in MIS-C, and accordingly, a patient who did not respond to anti-inflammatory therapies was treated with the zonulin antagonist larazotide, with a satisfactory outcome¹⁵³. In a pooled metanalysis, D-dimer was found to be elevated in 92% of patients (330 out of 356)²¹¹. Because of the associated risk of hypercoagulability, and extrapolating from the management of Kawasaki disease, the use of anticoagulants such as acetylsalicylic acid and/or enoxaparin has been reported^{212,213}.

[H1]MIS-C: distinct from Kawasaki disease?

Both Kawasaki disease and MIS-C have temporal associations with infectious diseases and are associated with immune-system alteration, systemic inflammation and cytokine storm. Myocardial dysfunction, which is seen in both pathologies, might be a consequence of systemic inflammation^{214,215}. An artificial intelligence computational analysis based on viral pandemics and disease-severity gene signatures, and in particular induction of *IL15–IL15RA*-specific genes, has placed Kawasaki disease and MIS-C on the same host-immune-response continuum (although these results have not yet been peer reviewed)²¹⁶. Consistently, patients with MIS-C have significantly higher levels of IL-15 than paediatric COVID-19-affected patients¹⁹⁰. However, the intensity of the immune response is high in MIS-C, which places it further along the severity spectrum than Kawasaki disease²¹⁶.

A quarter to half of patients with MIS-C meet the full criteria for diagnosis of Kawasaki disease^{17,149,150,213,217}. Without evidence of prior SARS-CoV-2 exposure in these patients, it might not be possible to differentiate them from those with classic Kawasaki disease. Commonly reported clinical features of MIS-C include fever, mucocutaneous findings, myocardial dysfunction with cardiogenic or vasoplegic shock, gastrointestinal symptoms, and neurological features including headache and altered mental status (**Table 4**). Like Kawasaki disease, these clinical manifestations are not specific to MIS-C, and they could occur in other infectious or inflammatory conditions¹¹⁵.

[H2]Epidemiological and clinical differences

Despite the apparent similarities between MIS-C and Kawasaki disease, there are important epidemiological and clinical differences^{20,123,128}. Kawasaki disease is typically a disease of young children <5-years old, whereas MIS-C has been reported in a wide age range from 1.6 to 20 years, with a median age of 6–11 years (**Table 2**)^{20,218,219}. In a sharp contrast to Kawasaki disease, there is a surprising lack of reports of MIS-C from Japan and East Asian countries^{220,221}. In fact, published data from the USA and Europe suggest that MIS-C is most commonly encountered in children of African and Hispanic heritage^{178,181}. These epidemiological differences suggest that although MIS-C has phenotypic similarities to Kawasaki disease, they are essentially distinct syndromes.

Cardiac involvement is more prevalent and severe in MIS-C than in Kawasaki disease. Although a quarter of untreated patients with Kawasaki disease will develop coronary artery abnormalities, in the current era with a high level of clinical suspicion as well as early diagnosis and treatment, the incidence of coronary artery abnormalities in Kawasaki disease is <10%^{217,222–225}. By contrast, our understanding of coronary artery dilation in MIS-C is still evolving, and incidence rates of 14–48% have been reported in various patient populations (FIG. 3)^{181,192,193}. However, the adoption of standardized MIS-C management protocols has begun to reduce the rate of coronary artery involvement¹⁵⁰. Cardiac MRI in MIS-C has demonstrated high signal intensity on T1-weighted and T2-weighted imaging, consistent with diffuse myocardial oedema, with no enhancement on late gadolinium imaging to suggest fibrosis²²⁹. Results from echocardiographic studies have demonstrated that global left ventricular longitudinal strain is significantly lower in individuals with MIS-C than in those with Kawasaki disease²³⁰. A longitudinal, single-centre study involving 15 children with MIS-C has demonstrated significant improvement towards normalization of both ventricular function and coronary artery size over a 30-day follow-up period²³¹.

Fewer than 10% of cases of Kawasaki disease manifest as Kawasaki disease-shock syndrome (KDSS), which requires the use of intravascular fluid resuscitation and vasoactive medication^{232–235}. Patients with KDSS tend to be older, have longer duration of fever and higher levels of inflammatory markers, and have a higher incidence of IVIG resistance as well as coronary abnormalities than those without KDSS^{236,237}. By contrast, shock and depressed left ventricular systolic function are more frequent with MIS-C, for which reports indicate that 40–

80% of patients present with shock (FIG. 3)^{211,226–228}. In a retrospective comparison of a cohort of patients with KDSS with published data relating to MIS-C, individuals with KDSS were more likely than those with MIS-C to fulfil the diagnostic criteria for complete Kawasaki disease, with higher incidence of coronary artery aneurysms²³⁸.

Kawasaki disease has been reported to occur with MAS^{239,240}. In a retrospective analysis of 638 patients with Kawasaki disease, the incidence of MAS was <2%²⁴¹. However this figure is likely to be an underestimation of the true incidence, resulting from an absence of sensitive diagnostic criteria and a lack of awareness among health-care providers²⁴². Patients with Kawasaki disease and MAS tend to have elevation of levels of IFN γ , TNF, serum neopterin, IL-18 and sTNFR-II²⁴³. A retrospective comparison of patients with MAS (as a complication of systemic-onset juvenile idiopathic arthritis) and MIS-C revealed that MAS was associated with lower levels of haemoglobin and fibrinogen, and higher ferritin and lactate dehydrogenase, whereas patients with MIS-C tended to have signs of shock and need of intensive-care management²⁴⁴. Results that have not yet been peer reviewed, based on analyses of IFN γ and CXCL9 signalling characteristics, suggest that >50% of patients with MIS-C have a MAS-like cytokine phenotype¹⁹¹, along with elevation of CD163, IL2RA and ferritin (during the early period) in the plasma. However, although MAS has an association with neutropenia, patients with MIS-C, including those who meet the criteria for MAS, display neutrophilia. Thus, although KDSS and Kawasaki disease with MAS have overlapping clinical features with MIS-C, there are subtle differences that are likely to reflect the different cytokine profiles in these conditions.

Gastrointestinal and neurological symptoms are also more commonly encountered in MIS-C than in Kawasaki disease^{135,227,228,245–248}. The gastrointestinal manifestations include abdominal pain, vomiting and diarrhoea^{211,227,248}, with rare presentations that resemble appendicitis requiring surgical exploration²⁴⁹. In a national US registry consisting of 1,695 children and adolescents with active COVID-19 infections including MIS-C, neurological symptoms were noted in 22% of the patient population ($n = 365$), with most of those affected having transient symptoms²³⁷. In the patients with neurological involvement, 126 (35%) met the criteria for MIS-C, 43 (12%) had life-threatening neurological involvement (including encephalopathy, stroke, central nervous system infection/demyelination, Guillain–Barré syndrome and acute cerebral oedema) and 20 (5%) had life-threatening neurological involvement and met the criteria for

MIS-C. In a study of 286 children with MIS-C located in 55 centres in 17 European countries, neurological involvement was identified in 43 individuals (15%)²²⁷. In a pooled meta-analysis of data from 370 children with MIS-C, 133 (35.9%) had neurological symptoms (**Table 4**)²¹¹. Neurological involvement in Kawasaki disease is variable, reportedly affecting 5–39% of patients^{250,251}.

In contrast to Kawasaki disease, patients with MIS-C tend to have a worse acute clinical course and multisystem involvement, as illustrated by an increased requirement for intensive-care management. A large study of >1,000 patients with Kawasaki disease revealed that 2.4% of these children required intensive care²⁵². In stark contrast, an analysis of 783 cases of MIS-C determined that 68% of patients required intensive-care admission, 63% needed inotropic support, 28% had some form of respiratory support, and 4% of patients required extra-corporeal membrane oxygenation²⁵³. Among 1,080 patients with MIS-C, intensive-care admission was more likely in children aged >5-years old than in younger children, and in non-Hispanic Black patients than in non-Hispanic White patients, and coronary artery abnormalities were more common in boys than in girls²⁵⁴. Elevated acute-phase inflammatory markers, troponin, B-type natriuretic peptide and D-dimer levels also identified patients at risk of severe disease²⁵⁴. In a study evaluating 29 children with MIS-C in France, severe disease occurred in 52% of them, and was associated with high persistent fever and high levels of inflammatory markers²⁵⁵. Although the reason for a more critical illness in the acute phase of MIS-C than in Kawasaki disease is unclear, it is thought to be linked to the cytokine storm in MIS-C.^{256,257}

[H2]Immunological differences

In several small studies, comparative immune profiling of children with MIS-C and Kawasaki disease has been performed, to differentiate between these two disease entities. MIS-C is associated with lymphopenia, lower white-blood-cell and naïve CD4⁺ T-cell counts, and increased central and effector memory T-cell subpopulations, compared with Kawasaki disease¹⁰³. IL-17 is a mediator of inflammation in Kawasaki disease, but is less prominent in MIS-C¹⁰³. In a comparison of cytokine profiles, levels of circulating IFN γ were significantly higher in patients with severe forms of MIS-C than in those with milder MIS-C and Kawasaki disease²⁵⁸.

In a study of the immunological profiles of paediatric patients, 75% of those with MIS-C, but none with Kawasaki disease, TSS or COVID-19, displayed non-HLA biased, SARS-CoV-2

non-reactive, polyclonal expansion of TCR V β 21.3⁺ activated CD4⁺ and CD8⁺ T cells¹⁶⁶. Notably, these V β 21.3⁺ T cells had high expression of CX3CR1, a marker previously identified on the activated CD8⁺ T cells of MIS-C patients¹⁸⁶. The remarkable specificity of V β 21.3⁺ T-cell subset expansion noted in MIS-C is consistent with superantigen-mediated activation of the immune system¹⁶⁴, whereas in Kawasaki disease, evidence for a role of superantigens in pathogenesis is lacking⁵⁰.

Autoantibody profiles have been compared in patients with MIS-C and Kawasaki disease¹⁰³. Levels of antibodies to some vascular endothelial-cell proteins, such as endoglin, were higher in both groups of patients than in healthy controls, whereas some autoantibodies (such as that to EGF-like repeat and discoidin I-like domain-containing protein 3) were overexpressed in Kawasaki disease compared with MIS-C. To confound matters, plasma levels of endoglin were elevated in both sets of patients compared with healthy children, raising the possibility that antibodies to endothelial cells were the result of vascular damage rather than the cause. Another possibility is that the S protein superantigen of SARS-CoV2 might cause aberrant activation of B cells¹⁶³.

Some laboratory parameters are important differentiators between Kawasaki disease and MIS-C. Although both syndromes involve a diffuse hyper-inflammatory response, patients with MIS-C tend to have a lower platelet count, lower absolute lymphocyte count and higher levels of C-reactive protein, N-terminal pro-B-type natriuretic peptide, troponin and ferritin^{16,17,94,100-115,165}. Additionally, coagulation abnormalities are common, including elevation of D-dimer and fibrinogen levels^{11,12,257,259}. Hyponatraemia is another common laboratory finding in patients with MIS-C¹²⁸. The presence of burr cells and neutrophils with toxic granulation can also discriminate MIS-C from severe COVID-19¹⁵¹. Finally, evidence of recent SARS-CoV-2 infection, particularly by positive serology, is a diagnostic indicator of MIS-C^{149,150}.

[H1]Conclusion

Epidemiological and clinical differences reveal that although MIS-C has phenotypic similarities to Kawasaki disease, they are different syndromes. They have varying degrees of hyperinflammation and dysregulated immune responses¹³². Children with MIS-C are, in general, more critically ill, with prominent gastrointestinal symptoms, cardiac involvement with shock, haematological abnormalities and elevated acute-phase reactants. They have positive SARS-

CoV-2 serology, suggesting a link to prior clinical or subclinical infection or exposure. It is likely that a combination of pathogen and host factors is involved in the genesis of an intense aberrant activation of both innate and adaptive immune responses and subsequent cytokine storm^{16,18}. Some of the pathogen-related factors include antigen mimicry of host antigens, and superantigen properties of viral proteins. Potential host factors include age and immune-system immaturity, altered intestinal microbiota, nutritional deficiencies and genetic (including inborn errors of immunity) and epigenetic predisposition¹³. However, to what extent each of these factors contributes, and how they interact to cause the clinical syndrome, are relative unknowns that need further exploration. Various lines of evidence based on inflammatory parameters, clinical signs or gene analyses have evoked the possibility that MIS-C is a heterogenous complex disorder. Current data on the immune signatures in patients with MIS-C are based on small sample size, non-homogenous cohorts. Hence, analysis of dynamic changes in the immune signatures of patients with MIS-C and their comparison with Kawasaki disease in a large homogenous cohort is needed, to accurately determine the similarities and distinct features of the two disease entities. Nevertheless, with the evidence of elevation of signatures of autoimmunity in MIS-C, and reports of various post-COVID-19 conditions in adults, long-term follow-up of patients with MIS-C might be advisable, because of the possibility of relapse. Notably, however, relapse is rare in Kawasaki disease, which might suggest that recurrence is also unlikely in MIS-C.

While researchers and clinicians navigate the possibilities and evaluate the best treatment options for patients affected by COVID-19-related illnesses, it is imperative to establish registries and dedicated multidisciplinary research teams to investigate the pathogenesis and specific therapeutic strategies in MIS-C. An important step towards this end was the workshop that was convened by the NIH in June 2020, which aimed to bring together the experts on the subject, to initiate dialogue leading to future studies²⁶⁰. In conclusion, MIS-C has important epidemiological, clinical and immunological differences from Kawasaki disease, enabling its classification as a separate syndrome. Study of MIS-C will continue to enhance our understanding of these conditions that are related by their association with the cytokine storm phenomenon.

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C.S., M.G. and J.B. researched data for the article. C.S., M.G. and J.B. wrote the article. All authors provided substantial contribution to discussion of the content, and reviewed and approved the text before submission.

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Key points

- Multisystem inflammatory syndrome in children (MIS-C) is characterized by exaggerated innate and adaptive immune responses following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in predisposed children
- Clinical presentation of MIS-C involves multiple organ systems, with prominent involvement of the gastrointestinal and cardiovascular systems
- The factors that trigger the development of MIS-C in children exposed to or infected with SARS-CoV-2 are not yet known
- Results from epidemiological, clinical and immunological investigations have revealed that although MIS-C has phenotypic similarities to Kawasaki disease, they are different syndromes

Comparison	Kawasaki disease	MIS-C
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- The approach to treatment of MIS-C aims to mute the augmented inflammatory response

Table 1 | Comparison of Kawasaki disease and MIS-C

Demographics		
Age	6 months to 5 years	6–11 years
Sex	Male predominance (~1.5:1)	No apparent predominance
Race or ethnicity	Highest incidence in Japan, China, South Korea and Taiwan	Highest incidence in children of African and Hispanic heritage
Pathogenesis		
Trigger	Unknown but some data suggest possible preceding viral or bacterial infection	Onset ~3–6 weeks post SARS-CoV-2 exposure
Immunological characteristics		
Similarities	Enhancement of IL-1 β ⁺ neutrophils and immature neutrophils	
Differences	T-cell activation by a conventional antigen	SARS-CoV-2 viral S protein acts like a superantigen, triggering a cytokine storm
	High levels of IL-17	High levels of IL-15, IFN γ in severe cases
	Relatively less frequent MAS-like cytokine profile	>50% of patients with MIS-C have a MAS-like cytokine phenotype
	Lymphopenia is rare	Lymphopenia
	Anti-SARS-CoV-2-IgG-not reported	Anti-SARS-CoV-2-IgG
Clinical features		
Similarities	Similar associations with fever, rash, cervical lymphadenopathy, neurological symptoms, extremity changes	
Differences	Relatively high incidence of conjunctival injection and oral mucous membrane changes	Relatively high incidence of gastrointestinal symptoms, myocarditis and shock, and coagulopathy
Management		
Common	IVIg, glucocorticoids, acetylsalicylic acid	IVIg, glucocorticoids, acetylsalicylic acid
Rare	Infliximab, ciclosporin and anakinra	Anakinra, tocilizumab

IVIg, intravenous immunoglobulin; MAS, macrophage activation syndrome; MIS-C; multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 2 | Demographic features of MIS-C study populations

Study	Cohort location	N	Median age (range or IQR)	Male:female	Race or ethnicity	Reference
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				(%)		
Dufort et al.	USA	99	No median. Distribution: 0–5 years, 31%; 6–12 years, 42%; 13–20 years, 26%	54:46	Black, 40%; white, 37%; Hispanic, 36%; other, 18%; Asian, 5%	¹⁴
Cheung et al.	USA	17	8 years (1.8–16 years)	47:53	Ashkenazi Jewish, 35%; Black, 24%; Hispanic, 24%; white non-Hispanic, 12%; Asian, 6%	¹⁵
Belhadjer et al.	France, Switzerland	35	10 years (2–16 years)	51:49	Not reported	¹²³
Kaushik et al.	USA	33	10 years (IQR 6–13 years)	61:39	Hispanic, 45%; Black, 38%; white, 9%; Asian, 3%; other, 3%	¹²⁶
Davies et al.	UK	78	11 years (IQR 8–14 years)	67:33	Afro-Caribbean, 47%; Asian, 28%; white, 22 %; other, 3%	¹²⁷
Pouletty et al.	France	16	10 years (IQR 4.7–12.5 years)	50:50	Not reported	¹²⁸
Toubiana et al.	France	21	7.9 years (3.7–16.6 years)	43:57	Sub-Saharan African/Caribbean parentage, 57%; European parentage, 29%; Asian parentage, 10%; Middle Eastern parentage, 5%	¹²⁹
Capone et al.	USA	33	8.6 years (IQR 4.4–12.6 years)	61:39	Other, 45%; Black, 24%; Asian, 9%; white, 9%; Unknown, 12% [Hispanic, 27%; non- Hispanic, 73%]	¹³⁰
Hameed et al.	UK	35	11 years (IQR 6–14 years)	77:23	Not reported	¹³¹
Whittaker et al.	UK	58	9 years (IQR 5.7–14 years)	56:44	Black, 38%; Asian, 31%; white, 21%; other, 10%	¹³²
Moraleda et al.	Spain	31	7.6 years (IQR 4.5–11.5 years)	58:42	Not reported	¹³³

Dhanalakshmi et al.	India	19	6 years (1.1–16.9 years)	42:58	Not reported	134
Miller et al.	USA	44	7.3 years (0.7–20 years)	45:55	Hispanic, 34%; not reported, 25%; white, 20.5%; Black, 20.5%	135
Belot et al.	France	108	8 years (IQR 5–11 years)	49:51	Not reported	136
Lee et al.	USA	28	9 years (0.1–17 years)	57:43	Hispanic, 43%; white, 36%; Black, 18%; not reported, 3%	137
Riollano-Cruz M et al.	USA	15	No median. Mean 12 years (3–20 years)	73:27	Hispanic, 66%; non-Hispanic African American, 13%; non-Hispanic white, 13%; other, 8%	138
Ramcharan et al.	UK	15	8.8 years (IQR 6.4–11.2 years)	73:27	African or Afro-Caribbean, 40%; South Asian, 40%; mixed, 13%; other, 7%	139
Grimaud et al.	France	20	10 years (2–16 years)	50:50	Not reported	140
Perez-Toledo et al.	UK	8	9 years (7–14 years)	63:37	Not reported	141
Jonat et al.	USA	54	7 years (0.7–20 years)	46:54	White, 35%; unknown, 31%; other, 19%; African American, 15%	206
Feldstein et al.	USA	186	8.3 years (IQR 3.3–12.5 years)	65:35	Hispanic, 31%; Black, 25%; unknown, 22%; white, 19%; other, 5%	13
Toubiana et al.	France	23	8.2 years	52:48	Not reported	228
García-Salido A et al.	Spain	61	9.4 years (IQR 5.5–11.8 years)	66:34	Not reported	146
Shobhavat et al.	India	21	7 years (IQR 1.9–12.1 years)	47:53	Not reported	268
Niño-Taravilla et	Chile	26	6.5 years (IQR 2–10.5 years)	58:42	Chilean, 73%; Venezuelan, 12%;	269

al.					Peruvian, 8%; Colombian, 4%; Haitian, 4%	
Tolunay et al.	Turkey	52	9 years (IQR 5–13 years)	38:62	Turkish, 86%; Syrian, 14%	²⁷⁰

IQR: interquartile range; MIS-C; multisystem inflammatory syndrome in children

Table 3 | Treatment of MIS-C

Study	Cohort location	N	IVIg	Glucocorticoids	Other treatments	Reference
Dufort et al.	USA	99	70%	64%	NR	¹⁴
Cheung et al.	USA	17	77%	82%	Tocilizumab, 6%	¹⁵
Belhadjer et al.	France, Switzerland	35	72%	34%	Anakinra, 9%	¹²³
Kaushik et al.	USA	33	54%	51%	Tocilizumab, 36%; remdesivir, 21%; anakinra, 12%; convalescent plasma therapy, 3%	¹²⁶
Davies et al.	UK	78	76%	73%	Tocilizumab, 4%; anakinra, 10%; infliximab, 9%; rituximab, 1%	¹²⁷
Pouletty et al.	France	16	94%	18.8%	Tocilizumab, 6%; anakinra, 6%; hydroxychloroquine, 6%	¹²⁸
Toubiana et al.	France	21	100%	33%	NR	¹²⁹
Capone et al.	USA	33	100%	70%	Tocilizumab, 9%; anakinra, 12%; infliximab, 3%	¹³⁰
Hameed et al.	UK	35	100%	100%	NR	¹³¹
Whittaker et al.	UK	58	71%	64%	Anakinra, 5%; infliximab, 14%	¹³²
Moraleda et al.	Spain	31	65%	68%	Remdesivir, 6%	¹³³
Dhanalakshmi et al.	India	19	79%	58%	Tocilizumab, 5%	¹³⁴

Miller et al.	USA	44	82%	96%	Anakinra, 18%	135
Lee et al.	USA	28	71%	61%	Anakinra, 18%	137
Riollano-Cruz et al.	USA	15	80%	20%	Tocilizumab, 80%; remdesivir, 13%; anakinra, 13%; convalescent plasma therapy, 6%	138
Ramcharan et al.	UK	15	66%	33%	NR	139
Grimaud et al.	France	20	100%	10%	Tocilizumab, 10%; anakinra, 10%	140
Jonat et al.	USA	54	83%	79%	NR	206
Feldstein et al.	USA	186	77%	49%	Anakinra, 13%	13
Toubiana et al.	France	23	100%	61%	NR	228
García-Salido et al.	Spain	61	45%	80%	Tocilizumab, 24%; hydroxychloroquine, 55%	146
Shobhavat et al.	India	21	52%	86%	Tocilizumab, 10%	268
Niño-Taravilla et al.	Chile	26	77%	88%	Tocilizumab, 12%; infliximab, 4%	269
Tolunay et al.	Turkey	52	93%	71%	Anakinra, 4%	270

IVIG, intravenous immunoglobulin; MIS-C; multisystem inflammatory syndrome in children; NR, not reported

Table 4 | Reported clinical features of multisystem inflammatory syndrome in children

Affected organ system	Symptoms	Frequency of involvement	References
Cardiovascular	Shock	40–80%	211,226–228
	Cardiac arrhythmias	2%	227
	Abnormal ST- or T-wave segment	22%	227
	Prolonged QT interval	2%	227
	Pericardial effusion	13–28%	227,248
	Decreased LVEF by echo	31–58%	226,227
	Increased troponin	68–95%	226,227
	Myocarditis	36–87%	211,228,248
	Coronary artery dilatation on CT	27%	227
	Coronary artery aneurysm	14–48%	226–228

	Mild	22%	227
	Moderate	7%	227
	Giant	1%	227
Gastrointestinal	Gastrointestinal symptoms	60–100%	226–228
	Diarrhoea	38–72%	211,227
	Vomiting	51–68%	211,248
	Abdominal pain	19–71%	211,227
	Ascites	21%	227
	Ileitis	9%	227
	Colitis	4%	227
Ophthalmologic	Conjunctivitis	32–83%	226– 228,248,261
	Periorbital erythema and oedema	20%	261
Nervous system	Neurological symptoms	13–35%	211,227,228,271
	Severe symptoms, including encephalopathy, stroke, central nervous system infection/demyelination, Guillain–Barré syndrome and acute cerebral oedema	5%	271
Integumentary	Rash	50–70%	226,228,248
	Erythematous skin rash	62%	227
	Hyperaemia, oedema or desquamation of extremities	26–51%	227,261
	Malar erythema	17%	261
	Skin eruptions	9–14%	261
	Desquamation in groin	26%	228
Respiratory	Upper respiratory tract infection	34%	227
	Lower respiratory tract infection	22%	227
	Pleural effusion on CT	20%	227
	Lung involvement on CT (bilateral pulmonary consolidation and ground-glass opacity)	13%	227
Mucosal	Oral mucosa hyperaemia	41%	227
	Red and/or cracked lips	37–49%	248,261
	Strawberry tongue	11–23%	248,261
	Lips and oral-cavity changes	74%	226,228
Other	Lymphadenopathy (cervical)	19–61%	227,228,248
	Extremity changes	8–52%	226,228,248

LVEF, left ventricular ejection fraction

Figure 1 | The temporal relationship between SARS-CoV-2 infection and development of MIS-C. Evidence suggests that a relationship exists between the timing of SARS-CoV-2 infection and development of multisystem inflammatory syndrome in children (MIS-C). Cases of MIS-C tend to be seen 3–6 weeks after the peak of SARS-CoV-2 transmission in a community. Because of this time lag, MIS-C is associated with a strong anti-Spike protein IgG response, but a weak IgM response. It should be noted that implication of SARS-CoV-2 as a triggering factor for the development of MIS-C is yet to be firmly established.

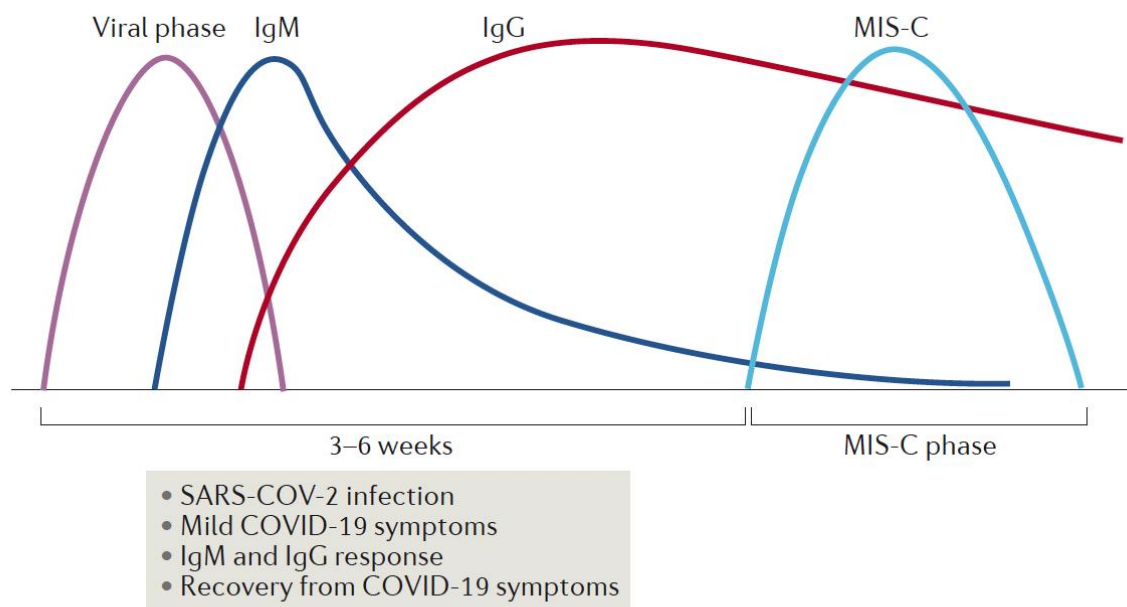


Figure 2 | Possible mechanisms implicated in aberrant activation of immune cells in MIS-C. Clinical signs of multisystem inflammatory syndrome in children (MIS-C) mostly appear several weeks after SARS-CoV-2 infection. MIS-C might be triggered by dysregulation of immune responses following viral infection. Aberrant activation of immune cells in patients with MIS-C could result from several factors. Infection with particular variants of SARS-CoV-2 might trigger hyperinflammatory responses. Genetic predisposition resulting from variants in the genes encoding pattern recognition receptors, Fc γ receptors and components of the signalling cascades of immune response, as well as mutations in genes such as *SOCS1*, which regulate inflammatory responses, could all contribute to enhancement of inflammatory responses to infection. Dysregulated activation of lymphocytes, with production of IgG corresponding to microbial

pathogens or autoantigens, could cause immune-complex-mediated innate-cell activation by signalling via Fcγ receptors. Production of autoantibodies could also lead to complement activation and autoantibody-mediated endothelial damage. SARS-CoV-2 S protein might function as a superantigen, contributing to activation of T cells. Abbreviations: SOCS1, suppressor of cytokine signalling 1; TLR, Toll-like receptor.

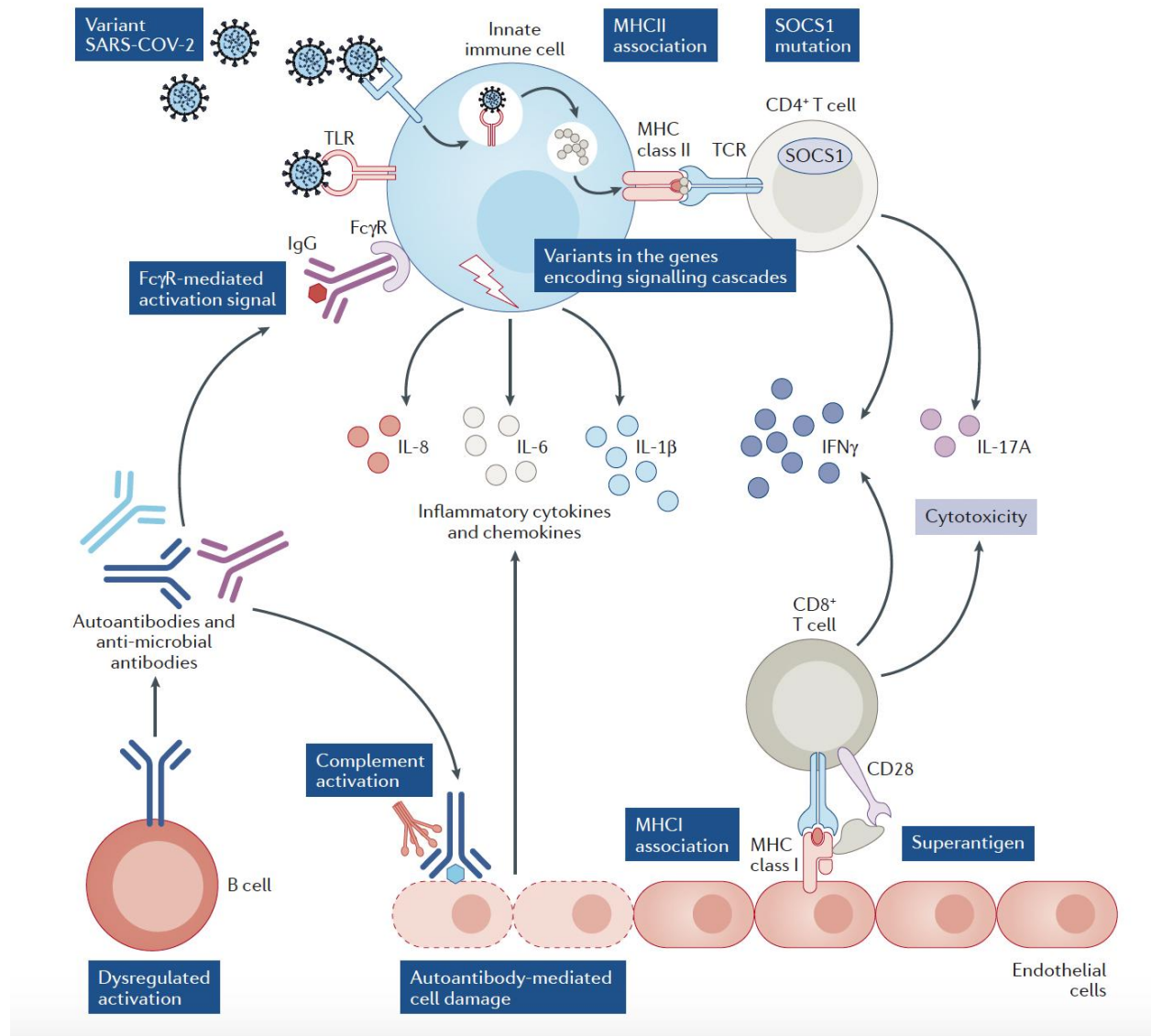


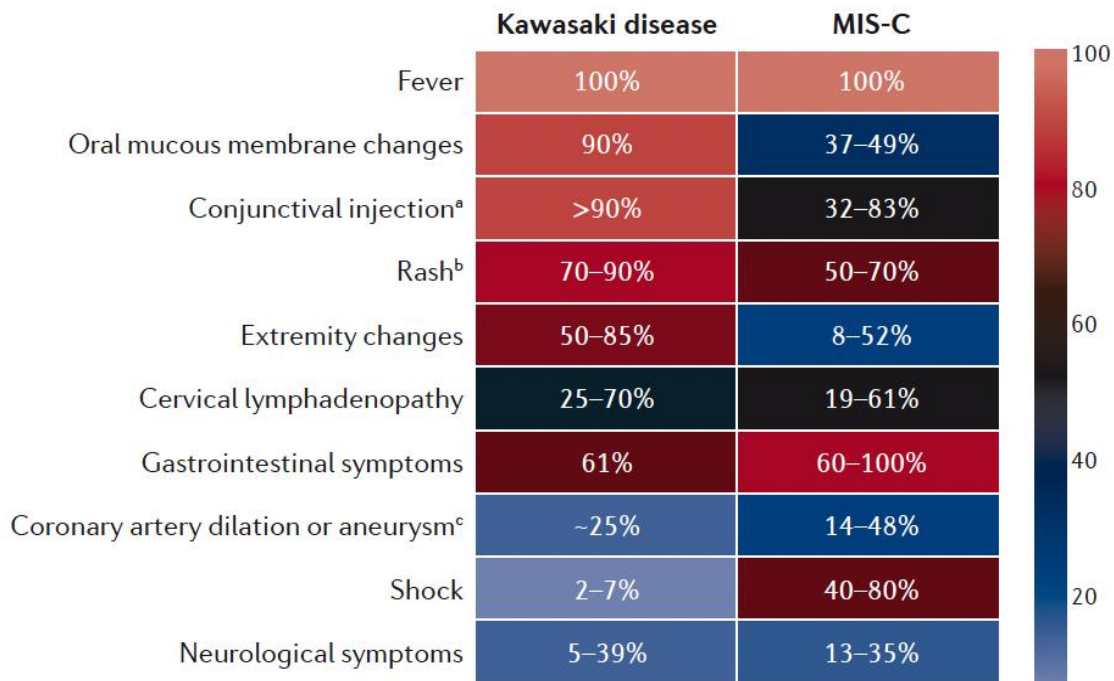
Figure 3 | Comparative incidence of clinical signs in MIS-C and Kawasaki disease. Percentage incidence of particular symptoms in patients with multisystem inflammatory

syndrome in children (MIS-C) or Kawasaki disease is shown, with the values derived from published reports^{211,226-228,235,236,248,250,261-267}. Although some clinical signs, such as fever and cervical lymphadenopathy are equally prevalent in both MIS-C and Kawasaki disease, the incidence of other symptoms, including shock, coronary artery involvement and gastrointestinal symptoms (vomiting, diarrhoea or abdominal pain), are characteristic of MIS-C.

^a‘Conjunctival injection’ refers to bilateral nonexudative conjunctivitis in Kawasaki disease

^b‘Rash’ refers to polymorphous rash in Kawasaki disease

^c‘Coronary artery dilation of aneurysm’ refers to incidence in untreated cases of Kawasaki disease



ToC blurb

In this timely Review, the authors compare and contrast two forms of childhood inflammatory vasculitis; Kawasaki disease and the COVID-19-associated multisystem inflammatory syndrome in children, highlighting epidemiological, clinical and immunological differences that suggest they should be classified as distinct syndromes.