

2024

Kawasaki disease: an ongoing enigma with parallels to COVID-19-related multisystem inflammatory syndrome in children

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BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**KAWASAKI DISEASE:
AN ONGOING ENIGMA WITH PARALLELS TO COVID-19-RELATED
MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN**

by

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B.A., Carleton College, 2020

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2024

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ABSTRACT

Kawasaki disease (KD) is a rare pediatric illness of unknown origin that causes high fever, acute inflammation of the blood vessels, and acquired heart conditions. Although multiple aspects of KD remain largely elusive, recent literature has detected an increasing number of KD-like cases among pediatric populations following severe acute respiratory syndrome 2 (SARS-CoV-2) infection, termed “multisystem inflammatory syndrome in children” (MIS-C). While similarities in certain clinical manifestations (fever, mucocutaneous disturbances, cardiac dysfunction, and skin rashes) have caused difficulties in distinguishing the two diseases, key differences in pathophysiology, etiology and epidemiology indicate they are distinct entities triggered by unique infectious agents. The two share commonalities in pathophysiology, characterized by hyperinflammation via cytokine storm. However, KD is notably associated with pathological changes in the coronary arteries, whereas MIS-C presents as a more exaggerated inflammatory syndrome causing myocarditis and ventricular dysfunction. Differences in age range, genetic predispositions, and ethnic distribution of patients has also been identified. Treatment strategies, namely intravenous immunoglobulin therapy (IVIG), have proven effective in both diseases, however MIS-C patients are reportedly

less responsive to IVIG and often require additional intervention methods. Distinguishing key characteristics in pathophysiology, etiology, and epidemiology not only helps in understanding differences in clinical manifestations, but also provides valuable insight into potentially unique diagnostic and therapeutic approaches to KD and MIS-C.

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LIST OF ABBREVIATIONS

ACE 2.....	Angiotensin-converting enzyme 2
AECA.....	Antiendothelial cell autoantibody
BLK.....	B lymphocyte kinase
CAA	Coronary artery aneurysm
CASP3.....	Caspase-3
CD.....	Cluster of differentiation
CDSN.....	Corneodesmosin
COVID-19.....	Caronavirus Disease 2019
CYBB.....	Cytochrome b-245 beta subunit
DC.....	Dendritic cell
DNA.....	Deoxyribonucleic acid
EBV.....	Epsteine-Barr virus
Fc.....	Fragment crystallizable region
GI	Gastrointestinal
HCoVNH	Human Coronavirus New Haven
HLA-1	Human leukocyte antigens class 1
HSPSG2	Heparan sulfate proteoglycan 2
IgA	Immunoglobulin A
IL.....	Interleukin
IP3.....	Inositol 1,4,5-trisphosphate
IVIG	Intravenous immunoglobulin

KD.....	Kawasaki Disease
MHC	Major histocompatibility complex
MIS-C	Multisystem Inflammatory Syndrome in Children
NET.....	Neutrophil extracellular trap
NFAT	Nuclear factor of activated T cells
ORAI1.....	Calcium release-activated channel protein 1
PGE2	Prostaglandin E2
RA.....	Receptor subunit alpha
RNA	Ribonucleic acid
ROS.....	Reactive oxygen species
RT	Reverse transcriptase
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Siglec.....	Sialic acid binding Ig-like lectin
SMAD3.....	Suppressor of mothers against decapentaplegic homolog 3
SNP	Single nucleotide polymorphism
SOCS1.....	Suppressor of cytokine signaling 1
STIM 1	Stromal interaction molecule 1
TGF- β	Transforming growth factor - β
TGF β R2	Transforming growth factor- β receptor type 2
Th17	T helper type 17 cell
TNF α	Tumor necrosis factor- α
T _{reg}	Regulatory T cell

TSS.....	Toxic Shock Syndrome
ViP	Viral pandemic
V β 21.3.....	β chain receptor variable region 21.3
XIAP	X-linked inhibitor of apoptosis

INTRODUCTION

Kawasaki disease (KD) is a rare pediatric systemic vasculitis of undetermined origin, often affecting children under five years of age. Although multiple aspects of this pediatric illness remain elusive, a novel clinical syndrome in children that emerged during the global pandemic of the coronavirus disease 2019 (COVID-19), termed “multisystem inflammatory syndrome in children” (MIS-C), has presented with comparable – and notably different – inflammatory characteristics that offers compelling insights into the clinical manifestations, immunological mechanisms, and management of both syndromes.

1. Clinical Manifestations

KD and MIS-C are both inflammatory disorders that lead to exaggerated symptoms along the same spectrum. Commonly reported clinical features in KD involve fever, mucocutaneous disturbances, cardiac dysfunction, and skin rashes. These clinical manifestations, however, are not distinct to KD and often occur in other inflammatory conditions, such as MIS-C. Despite overlapping clinical features, however, notable symptomatic differences suggest that these two entities are distinct diseases that result from unique immune dysregulation pathways (**Figure 1**). Distinguishing clinical characteristics between KD and MIS-C not only helps to guide diagnostic criteria, but also provides valuable insight into their potentially unique pathogenesis, etiology, and treatment strategies.

Cardiovascular

The hallmark of KD complications, particularly if left untreated, is the development of coronary artery aneurysms (CAAs). CAAs are defined as the enlargement of segments of the coronary artery due to weakening of vascular wall. While the exact mechanism for aneurysm is not fully understood, it is likely a result of immune complexes causing inflammation of the blood vessels.¹ Speculated pathological processes of CAA development will be discussed in detail later in this review.

Cardiac symptoms are more severe in MIS-C, in part due to an evolving understanding of the novel disease's clinical manifestations.² Despite high prevalence of CAAs in KD, in a current era of growing diagnostic and treatment strategies surrounding the disease, incidence of CAA complications <10%.^{2,3} This sharply contrasts the 14-48% incidence rates reported in MIS-C patient populations.^{2,4,5} Ventricular dysfunction is also a common cardiac complication observed in MIS-C. In their comparative cohort study of 503 MIS-C patients, Feldstein et al.⁶ reported 34.2% presented with decreased left ventricular function and left ventricular ejection fraction. Correlations of abnormal left ventricular function and cardiac inflammatory biomarkers, such as C-reactive protein and troponin, were recently detected by Gaitonde et al.⁷ Such findings highlight the presence of myocarditis in patients with MIS-C that likely results in cardiac myocyte apoptosis and subsequent ventricular dysfunction. Other cardiac manifestations of MIS-C include arrhythmia and conduction abnormalities, and hypotension.⁸ Prolonged states of MIS-C-

related cardiac inflammation can impair the ability of the heart to pump blood to vital organ systems, a condition known as cardiogenic shock.

The noteworthy differences in cardiac abnormalities between KD and MIS-C offer key insights into their potentially unique cytokine pathways through which MIS-C may trigger a more exaggerated host immune response.⁹

Pulmonary

Pulmonary presentation of KD is distinctly uncommon. In rare cases, pulmonary manifestations that have been documented in patients with KD have included pleural effusion (the entering of fluid into the pleural space) and bronchial pneumonia (inflammation of the bronchi). Symptoms of pulmonary effusion may be a result of increased vascular permeability from inflammation, resulting in decreased albumin levels and subsequent fluid escape in efforts to maintain concentration homeostasis.¹⁰ Reports of bronchial pneumonia are rare and have been associated with viral co-infections unrelated to KD.¹¹

Respiratory symptoms in MIS-C present very early and frequent. Tachypnea (fast breathing), desaturation (decreased blood-oxygen levels), and increased respiratory effort are among the most common clinical presentations.¹² While respiratory stress is rarely seen in KD patients, MIS-C patients requiring oxygen or mechanical ventilation ranges from 12-46% .¹³

Gastrointestinal

Gastrointestinal (GI) manifestations of KD and MIS-C can include vomiting, abdominal pain, and diarrhea. GI symptoms are more common in MIS-C than in KD, and are reportedly the second most involved organ system after the cardiovascular system in MIS-C patients.¹⁴ In their case study of 44 patients presenting with MIS-C, Miller et al.¹⁵ reported that 84.1% presented with GI symptoms, over a quarter (29.5%) of which had presented one week prior to hospitalization at an urgent care center for less severe symptoms mimicking viral gastroenteritis (e.g., nausea, vomiting, diarrhea). Abdominal imaging on 15 patients revealed inflammation of prominent GI organs, including the liver, stomach, small intestine, and colon.¹⁵

Cytokine-mediated inflammation in patients with MIS-C is speculated to affect the mesentery, peritoneum, and intestinal wall in a serosa-to-lumen (outer- to innermost tissue layer) manner. Severe GI symptoms observed in patients with MIS-C are speculated to result from the unique pathogenic mechanisms of SARS-CoV-2, which interact with receptors abundantly expressed in epithelial cells along the GI tract.¹⁶ The pathogenic mechanisms of SARS-CoV-2 will be discussed later in this review.

Mucocutaneous, Dermatological, Lymphatic

Hallmarks of KD involve mucocutaneous disturbances including cracked lips and a strawberry tongue. Involvement of the dermis is characterized by a rash on the hands and feet, as well as conjunctival hyperemia – causing redness of the eye due to inflamed

blood vessels. Other symptoms include lymphatic dysregulation such as palm and feet edema and cervical lymphadenopathy (swelling of the lymph nodes) greater than 1.5 cm.¹⁷

Similar clinical phenotypes are observed in MIS-C. Recent literature reviews have reported KD-like features in MIS-C patients, including skin rash (42%-58%), mucosal disturbances involving cracked lips and strawberry tongue (23%-59%), conjunctival hyperemia (40%-51%), edema of the hands and feet (15%), and cervical lymphadenopathy (4%-7%).^{17, 18} These findings illustrate one of the main reasons distinguishing between the two diseases can often be challenging in a clinical setting.

Neurological

Involvement of the nervous system in systemic inflammatory disorders is not uncommon. Although the exact prevalence of neurological symptoms in MIS-C is variable and lacks a clear epidemiological definition, it appears on average in 50% of MIS-C patients compared to 1%-30% of KD patients.¹⁹

Neurological manifestations in KD are considerably variable and poorly specific, ranging from headaches and meningism (neck stiffness) to sensorineural hearing loss and facial nerve palsy. In a recent retrospective case-control study by Lin et al.²⁰, children (< 5 years of age) with KD were nearly two times more likely than healthy controls to have

incidence of epilepsy. The authors speculate these epileptic trends could be a result of brain tissue injury linked to neuroinflammation.

Neurological phenotypes are more frequently encountered in MIS-C but remain poorly defined. Symptoms including headache, meningism, drowsiness, confusion, and severe encephalopathy (brain dysfunction). In their cohort study of 62 MIS-C children, Bova et al.²¹ identified 93% of patients presented with neurological involvement, 68% of which presented with mild and nonspecific symptoms while 26% were moderate-severe. Such symptoms are likely related to an extreme cerebral and vascular inflammatory response observed in MIS-C, whereby immunological hyperactivation following SARS-CoV-2 infection damages the blood-brain barrier and neuronal receptors. Hypoxia, secondary to impaired cardiovascular and pulmonary function, could also lead to neurological manifestations such as ischemic stroke.²⁰

Laboratory Markers

Elevated C-reactive protein (liver-derived protein produced in response to tissue damage), erythrocyte sedimentation (red blood cell clumping), and high white blood cell count are all observed during the acute stages of KD, and consistent with host inflammatory response. An increase in activated platelets – cell fragments that aid blood clotting – is also observed, and can lead to reactive thrombocytosis (overproduction of platelets) that causes blood clotting. A decrease in hemoglobin levels is also observed and is often associated with anemia in KD patients.²²

Laboratory markers during the acute phase of MIS-C are comparable to KD, except for a notable decrease in white blood cell count, termed leukopenia. Additional biomarkers of inflammation include troponin and brain natriuretic peptide.²³ The expansive profile of inflammatory markers detected in MIS-C are consistent with current understandings that MIS-C may trigger a more exaggerated host immune response relative to KD.

Immunological aberrations and their pathogenic roles in KD and MIS-C role will be discussed further in this review.

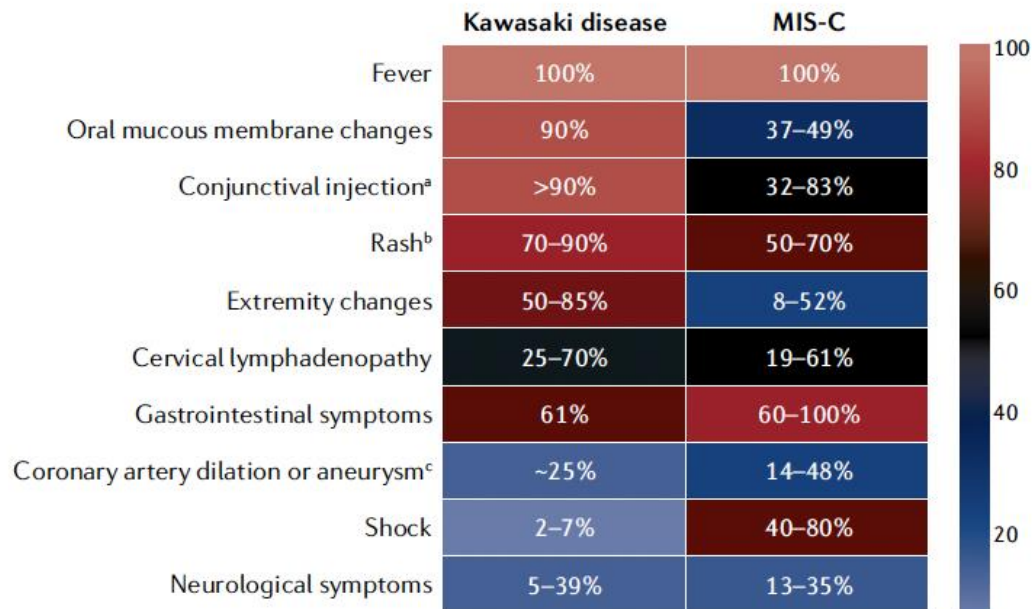


Figure 1. Comparative incidence of clinical manifestations in Kawasaki Disease and Multisystem Inflammatory Syndrome in Children. Incidence (%) of clinical phenotypes in patients with Kawasaki Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) is comparable in some capacities, such as fever and cervical lymphadenopathy (swelling of the lymph nodes), while incidence of other symptoms, including coronary artery involvement, gastrointestinal symptoms, and cardiogenic shock are characteristic of MIS-C. Figure from Sharma et al.²

2. Pathophysiology

KD is associated with coronary artery wall infiltration by various innate and adaptive immune cells. Rowley et al.²⁴ classifies the vascular pathology of KD into three consecutive and interconnected processes. Necrotizing arteritis develops within the first two weeks of the disease, often leading to aneurysm formation. This process is followed by two concurrent pathological phenomena, vasculitis (subacute or chronic), and proliferation of myofibroblasts – biomarkers of continuous early phase tissue repair in endothelial dysfunction. Myofibroblasts and their synthesized components slowly obstruct the coronary vessel and can limit natural blood flow, a process termed thrombosis. It should be noted, however, that thrombosis can occur during any point during this process due to decreased vascular integrity.^{24, 25}

The pathophysiology of MIS-C remains more elusive. Although cardiovascular impairment – specifically myocarditis and ventricular dysfunction – is the primary morbidity of MIS-C, the underlying mechanisms are still unclear.²⁶ Cases of MIS-C are generally seen 3-6 weeks after the peak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Delayed immune cell activation and the resultant cytokine storm results in a host of systemic hyperinflammatory responses in the lungs, intestines, endothelial cells, and cardiomyocytes. In general, the immune cells of MIS-C largely overlap with those of adults with SARS-CoV-2 rather than pediatric SARS-CoV-2.²⁶

2.1 Genetic Susceptibility

Single Nucleotide Polymorphisms

Genetic studies have recently offered insight on the role of single nucleotide polymorphisms (SNPs) and KD development. Four primary gene groups that have been identified with KD include caspase-3 (CASP3) associated with apoptosis, T cell activation, B cell signaling, and transforming growth factor- β (TGF- β).²

CASP3 encodes caspase-3, a protease that assists with apoptosis. In their molecular analysis, Onouchi et al.²⁷ found that a G to A substitution located in the 5' untranslated region of CASP3 prevented its ability to cleave essential nuclear factors that promote transcription of activated T cells. Defects in apoptotic regulation in T cells such as this could lead to a major role in downstream cytokine overproduction and the subsequent pathogenesis of KD-related inflammation.

Genes associated with T cell activation have also been associated with increased KD susceptibility. In their molecular analysis, Onouchi et al.²⁸ detected a notable SNP located in the coding region of the inositol-trisphosphate 3-kinase C (ITPKC) gene, which functions as a kinase of inositol 1,4,5-trisphosphate (IP3), to form IP4. IP3 is a secondary messenger molecule in various cell types, including T cells, that plays an important role in signal transduction of the Ca²⁺/nuclear factor of activated T cells (NFAT) pathway and subsequent cytokine production. The authors determined ITPKC as a negative regulator of the Ca²⁺/NFAT pathway that decreases T cell activation by modulating the amount of

IP3. Therefore, reduced ITPKC activity caused by the detected SNP may lead to enhanced IP3 levels and subsequent T cell activation associated with the pathogenesis of KD. A proposed model of ITPKC dysregulation in KD pathogenesis is demonstrated in **Figure 2**. Additional SNPs involved in the Ca^{2+} /NFAT pathway have recently been detected, including in genes encoding calcium release-activated calcium channel protein 1 (ORAI1) and stromal interaction molecule 1 (STIM 1) – both of which mediate T cell membrane activation and subsequent cytokine production.²⁷

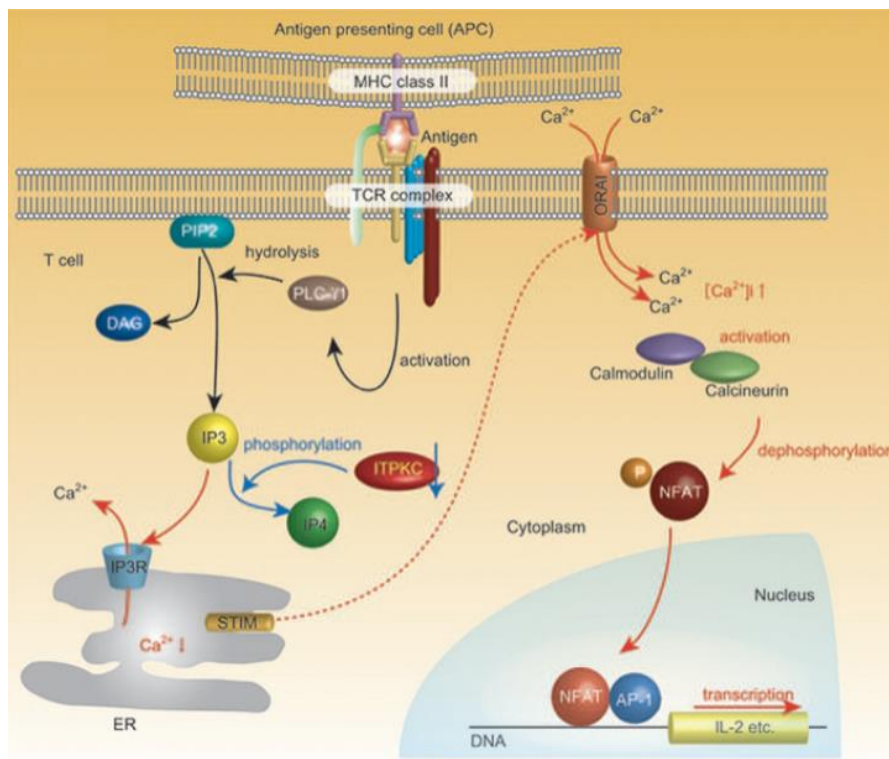


Figure 2. Proposed role of ITPKC as a negative regulator of Ca^{2+} /NFAT pathway in T cell activation. When the T cell receptor (TCR) is bound by an antigen/MHC complex II from an antigen presenting cell, IP₃ binds to its expressed receptor on the endoplasmic reticulum (ER) causing the release of Ca^{2+} . Depletion of intracellular ER Ca^{2+} levels stimulate Ca^{2+} -cytoplasmic entry via the stromal interaction molecule 1 (STIM 1). Increased cytoplasmic Ca^{2+} levels activate calcium-dependent calmodulin-calcineurin pathway, which results in the translocation of NFAT to the nucleus and subsequently drives transcription of genes important in T cell activation. ITPKC functions as a kinase

of IP3, deactivating its downstream effects. Therefore, reduced ITPKC activity caused by SNP may lead to enhanced IP3 levels and subsequent T cell activation associated with the pathogenesis of KD. Red arrows indicate molecules increased by ITPKC defect, while those reduced are represented by blue arrows. Figure adapted from Onouchi (2009).²⁸

Current literature has identified several KD susceptibility genes that are largely involved in B cell dysregulation and immunity. To date, genome-wide association studies have identified B lymphocyte kinase (BLK), heparan sulfate proteoglycan 2 (HSPG2), cluster of differentiation 40 (CD40), and corneodesmosin (CDSN).²⁹ Notably, these genes are all related to B cell development and function that may influence antibody type and production rate in response to an external trigger in patients with KD.

TGF- β is a multifunctional peptide that significantly contributes to cardiovascular remodeling and T cell activation, both of which are important components of KD. In their case-control molecular analysis, Shimizu et al.³⁰ identified SNPs in 6 genes in the TGF- β pathway that modestly influenced KD susceptibility. Among the SNPs identified, genetic variations in three specific genes, including TGF- β 2, TGF- β receptor type 2 (TGF- β R2), and Suppressor of Mothers against Decapentaplegic homolog 3 (SMAD3), consistently influenced occurrence of coronary artery aneurysms and aortic root dilation in patients with KD. TGF- β 2 is required for endocardial cushion cell transformation and has been observed to result in a variety of cardiovascular anomalies in knockout mice.^{30, 31} TGF- β R2 variation is linked to several aneurysm syndromes, suggesting the importance of this pathway in arterial modeling after KD.³² The third gene, SMAD3, plays an essential role

in the downregulation of T cells and arterial remodeling after injury³³; mutations in this gene suggest a susceptibility to KD pathogenesis and secondary coronary artery lesions.³⁰

MIS-C and KD Shared Host Immune Continuum

Abnormalities in inflammatory-related gene expression has been largely observed in patients with MIS-C. Major genetic variations that have been detected in MIS-C development include haploinsufficiency of suppressor of cytokine signaling 1 (SOCS1), defects in the X-linked inhibitor of apoptosis (XIAP), the beta subunit of cytochrome b-245 (CYBB), and specific human leukocyte antigens class I (HLA-1). Although these genetic risk factors vary from KD, similar expression of viral pandemic (ViP) signature genes – which determine the host response to viral infection – have been detected in both diseases and suggest a shared proximal pathway of immunopathogenesis.⁹

In their genetic analysis, Gosh et al.⁹ used the ViP signatures to compare host features between MIS-C and KD. The authors determined that both diseases are characterized by an interleukin (IL)-15 / IL-15 receptor subunit alpha (RA) cytokine storm. However, IL-15/IL-15RA genes were expressed at significantly higher levels in MIS-C relative to KD. Such findings suggest that while the host immune response is similar between the two diseases, the degree of response is more intense in MIS-C than KD, and may be accounted for by their unique genetic variants, among other factors.

A KD-specific transcript diagnostic signature, which is a unique group of mRNA sequences commonly used to identify children with KD, has also been used in recent molecular analyses to confirm a shared host immune response with MIS-C. In their validation, Gosh et al.⁹ found that the KD-specific transcript signature – comprised of various genes related to tumor necrosis factor- α (TNF α) and interleukin-6 (IL-6) pathways – could not differentiate between KD and MIS-C. These findings further confirm that the fundamental similarities between the two diseases at a molecular level.

2.2 Superantigens

Superantigens are defined as proteins that can result in excessive activation of the immune system. Specifically, these antigens can cause non-specific T cell activation via cross-linkage of their major histocompatibility complex (MHC) class II receptor and either the α or β chain of the T cell, resulting in a massive cytokine release (**Figure 3**).³⁴ While the exact pathogenic role of superantigens in both KD and MIS-C is uncertain, shared clinical features consistent with superantigen-mediated diseases, such as fever and rash, have caused them to be considered as potential triggers.

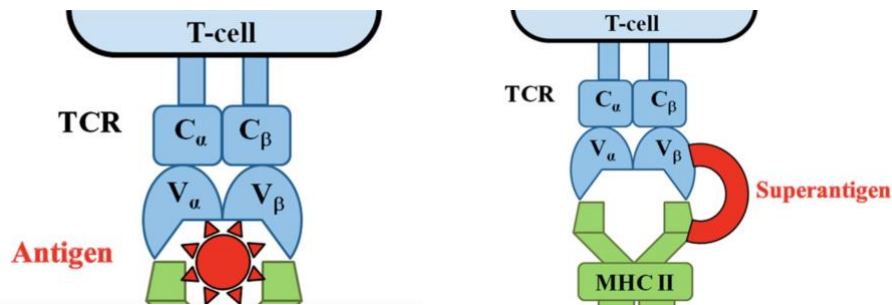


Figure 3. Conventional T cell activation and superantigen-mediated T cell activation. (Left) Conventional T-cell activation occurs between the antigen/MHC II complex of the antigen presenting cell (green) and the T-cell receptor (TCR) of the T cell. (Right) Superantigen-mediated T cell activation occurs via non-specific cross-linkage of the MHC II complex receptor and either the α or β chain of the TCR, resulting in a massive cytokine release. Figure adapted from Macias et al.³⁵

Recent literature has suggested that the SARS-CoV-2 viral S protein may have superantigen-like behavior. While its exact mechanism remains under investigation, it is speculated that the S protein contains a high-affinity region for T cell receptor binding that can trigger a cytokine storm and result in the development of toxic shock syndrome (TSS)-like presentation of MIS-C.¹⁶ The high-affinity binding region of the S protein displays structural similarities to the staphylococcal enterotoxin B, a superantigen that mediates TSS. To further investigate this concept, Hsieh et al.³⁶ studied T cell response to various SARS-CoV-2 peptides during the subacute phase of MIS-C in children. The authors found that there were numerous CD4⁺ and CD8⁺ T cells – lymphocytes that coordinate immune responses and kill virus-infected cells, respectively – bearing a particular variable region along the β chain of their receptor (V β 21.3) that were not present in the control SARS-CoV-2 T cell population. These findings are consistent with

the features of superantigens, which cross link variable regions of the T cell receptor β chains with MHC class II molecules on surface antigen presenting cells.

Whether the provoking antigen in KD is a conventional antigen or superantigen remains unclear. In their molecular analysis, Nagata et al.³⁷ identified superantigen activity in gut bacteria of KD patients. The authors hypothesized that supernatants of these bacteria can include T cell division and subsequent production of pro-inflammatory cytokines.

However, these findings have recently been disputed by several large-scale cohort studies that could not find evidence of superantigen-induced T cell receptor skewing when using flow cytometry.^{38, 39} Furthermore, patients with superantigen-mediated diseases present with severe gastrointestinal symptoms, cardiogenic shock, and neurological manifestations, all of which are more frequently reported during MIS-C than KD.¹⁶ Such findings suggest that KD is likely a product of T cell activation by a conventional antigen rather than a superantigen.

2.3 Immunological Aberrations

Neutrophils and NETs

An intense initial response in KD is driven by the innate immune system, particularly neutrophils. Neutrophils are short-acting granulocytes that serve as the immune system's initial defense against pathogens.⁴⁰ An early neutrophilic surge in KD results in the release of reactive oxygen species (ROS), which progressively destroys the innermost,

middle, and sections of the outermost tissue layer of the coronary artery. Destruction of critical elastic and smooth muscle components in the coronary vasculature ultimately leads to weakening of the blood vessel wall and subsequent aneurysm formation.⁴¹

The release of neutrophil extracellular traps (NETs) have also been implicated in the pathogenesis of KD. While NETs are understood to play a defensive role in the innate immune system through the release of intracellular granule components that capture and degrade infectious bacteria, recent literature has suggested its pathogenic potential in KD.²⁵ Yamashita et al.⁴¹ demonstrated that mice infected with human KD expressed significant neutrophil infiltration of the aortic root and coronary artery, leading to panvasculitis – an inflammatory response of the blood vessels that is consistent with KD autopsies. The neutrophils were found to express peptidylarginine deiminase 4, an essential enzyme of NET production. The authors concluded that infiltrative neutrophils in KD are more likely to produce NETs, which may lead to an uncontrolled inflammatory response causing tissue pathology. Mutua and Gershwin⁴² further expand on the pathological pathway of NETs in inflammatory diseases, speculating that non-specific granule components of NETs can recruit other pro-inflammatory cells, potentiate autoimmunity by delivering autoantigens to the host immune system, and promote thrombosis through their interactions with platelet-activated coagulation pathways. These are all pathological patterns consistent with KD.

There remains a paucity of literature examining the pathological role of neutrophils in MIS-C. Although neutrophil hyperactivation has been determined as a key component in severe COVID-19 in adults, the role of neutrophils in pediatric SARS-CoV-2 infections causing MIS-C remains more elusive. In their molecular analysis, Boribong et al.⁴³ examined neutrophil profiles in 152 children, including 43 children with COVID-19, 31 children clinically diagnosed with MIS-C, and 78 pediatric controls. The authors determined that the most highly upregulated genes in MIS-C neutrophils were those involving ROS production, neutrophil activation, and recruitment. The authors also found that the most elevated pathways in MIS-C neutrophils were metabolic, including oxidative phosphorylation and glycolysis, suggesting high cellular activity. Levels of spontaneous NETosis in MIS-C neutrophils were also significantly higher than pediatric COVID-19 and healthy control neutrophils. Interestingly, the authors performed a sub-analysis on MIS-C patients presenting with or without cardiac symptoms, including myocarditis, ventricular dysfunction, or coronary arterial aneurysms. Their findings showed that several hallmark genes of sepsis – an inflammatory response to infection – in cardiac MIS-C were enriched, including those that upregulate neutrophils. Such findings are consistent with previous literature that has detected activated neutrophils in the myocardium of autopsied patients with MIS-C, and suggest that that an upregulation of neutrophils is likely a key driver in the pathology leading to severe cardiac complications in these patients.⁴³⁻⁴⁵

Distinct neutrophilic phenotypes in MIS-C have been speculated to be a result of a unique mechanism. Unlike pediatric COVID-19, MIS-C patients do not present with a competent SARS-CoV-2 antigen in their blood. However, studies have detected viral ribonucleic acid (RNA) in MIS-C stool samples several weeks after infection. It is postulated that viral persistence is a result of increased gut permeability due to zonulin – a protein excreted by gut epithelial cells that disassemble tight cellular junctions – which permits viral antigen release into the bloodstream. Antigen exposure subsequently triggers neutrophil activation and NET formation within the vasculature.⁴⁶

T Cells

The role of T cells in KD has been largely scrutinized. As one of the major lymphatic components of the adaptive immune system, T cells function to recognize and defend against pathogenic antigens. T helper type 17 (Th17) cells activate immune cells like neutrophils and monocytes via pro-inflammatory IL-17; this leads to the production of inflammatory cytokines such as IL-1, IL-6, TNF, and IL-8. Alternatively, regulatory T (T_{reg}) cells suppress immune response through the release of anti-inflammatory cytokines like IL-10 and TGF- β . Recent literature has investigated an observed imbalance between T_{reg} and Th17 cells in patients with KD. When compared to healthy controls, Guo et al.⁴⁷ determined that patients with KD had significantly higher levels of IL-17 and IL-6, a cytokine profile which closely mirrors other autoimmune diseases like rheumatic arthritis. The authors also found that the KD cohort had lower levels of FoxP3 mRNA, a gene which controls expression of T_{reg}. Such findings suggest there exists a T_{reg}/Th17

imbalance which likely plays a role in KD pathogenesis, and that the immune response in KD shares a similar molecular profile with other autoimmune diseases.

Unlike KD, MIS-C is defined by lymphopenia (the reduction of lymphocytes), which can often be useful in lab profiling to discern the correct diagnosis. Despite patients with MIS-C present with pronounced CD4⁺ T cell lymphopenia, recent single-cell RNA sequencing analysis has revealed enhanced proliferation of these cells.⁴⁸ Such findings suggest that these cells are not apoptotic, but rather being shuttled to inflamed tissues and therefore undetected in blood samples. Another explanation for reduced lymphocytes is that the SARS-CoV-2 viral S protein may behave like a superantigen in MIS-C that compromises T cell response and expands a particular variable region along the β chain of its receptor, V β 21.3. Such mechanisms have been discussed earlier in this review. Despite lower lymphocyte levels, patients with MIS-C still present with increased relative levels of pro-inflammatory cytokines IL-1, IL-6 and IL-17 as found in KD, suggesting similarities exist between the diseases' T cell inflammatory mediator pathways.⁴⁹

B Cells

B cells function as a key regulatory cell in the immune system through the production of antibodies. Their pathogenic role in the development of KD, however, remains unclear. Current literature has identified several KD susceptibility genes discussed previously in this review that are largely involved in B cell dysregulation.²⁹

A growing body of literature on B cell involvement in KD has also investigated the role of antigen-specific immunoglobulin A (IgA) cells, an antibody derived from activated B cells.²⁴ IgA cells develop into plasma cells that play a key role in the defense of mucosal surfaces upon infectious exposure. Previous literature has determined ubiquitous IgA plasma-cell infiltration in patients with acute KD, including in the arterial wall, bronchi, and pancreas.⁵⁰ Interestingly, levels of IgA were decreased in the peripheral blood of acute KD patients relative to controls, suggesting these cells may selectively target tissues of the disease. The clonality of IgA genes in KD patients was further investigated by Rowley et al.⁵¹ to determine whether the antibodies were produced in response to a specific antigen. The authors found that the IgA cells in tissues inflamed by KD were oligoclonal, such that they produce a select repertoire of antibodies through an antigen-driven response.

MIS-C is characterized by a reduction of lymphocytes. Along with an observed reduction of T cells discussed earlier in this review, B cell cytopenia has also been reported. In their immunophenotype analysis of 25 MIS-C patients, Carter et al.⁵² determined that although neutralizing antibodies against SARS-CoV-2 were generated, patients had lower levels of total B cells, plasma cells (mature B cells that secrete antibodies), and class switched memory B cells (activated naïve B cells that have switched antibody expression), in their blood relative to healthy controls. Despite an overall reduction of B cells, MIS-C patients display an enrichment of IgA antibodies localized in endothelial, cardiac, and gastrointestinal tissue.⁵³ Although IgA antibody levels and tissue localization

appear similar to KD, it is unclear if MIS-C IgA antibody patterns are a result of a direct antigen-driven response or simply a downstream consequence of the disease. The authors speculate potential of the gut serving as a central point of SARS-CoV-2 infection in MIS-C, through which gastrointestinal inflammation – a result of increased permeability discussed earlier in this review – could drive IgA antibody levels.

Autoantibodies

Several studies have investigated the role of autoantibodies in the development of KD.⁵⁴ ⁵⁵ Autoantibodies ultimately develop due to a disruption in tolerance from self-antigens, through mechanisms including inflammation-mediated modification of self-antigens or cross-reactivity between foreign and self-antigens.⁵⁶ Due to the ubiquitous nature of self-antigens, a destructive cycle ensues through which autoantibodies fail to eliminate the antigen, causing inflammatory tissue response, subsequent self-antigen release, and further autoantibody production. Antiendothelial cell autoantibodies (AECAs) are a subtype of autoantibodies that attack endothelial cell antigens, causing endothelial cell damage and subsequent vasculitis symptoms consistent with KD.⁵⁶ Although the exact role of AECAs in the pathogenesis of KD remains unclear, serum samples of KD patients have directly revealed the presence of AECAs. Due to the expansive function of endothelial cells, the distinct antigenic targets of AECAs in KD have been proposed to affect a wide variety of vessels.⁵⁶

The role of autoantibodies in MIS-C remains more elusive. In their antibody array analysis, Consiglio et al.⁵⁵ screened serum samples of children with MIS-C and KD for individual autoantibody targets and identified endoglin, an endothelial-derived glycoprotein responsible for maintaining structural integrity of arterial walls, in both diseases. Despite detection of endoglin autoantibodies, the authors found plasma endoglin levels were elevated in MIS-C and KD patients relative to controls. Such findings suggest that autoantibodies to endoglin are not the cause of tissue damage – which would expectantly decrease endoglin levels – but rather, a consequence of tissue damage in response to heightened endoglin levels. Scant literature limits conclusions that can be drawn on the role of this autoantibody, and further studies are required to distinguish its role in disease pathogenesis or as a potential biomarker of endothelial damage.

Immune Complexes

While the role of immune complexes in KD has remained unclear for some time, the emergence of MIS-C amidst the most recent pandemic has caused their pathogenic role to be revisited. Immune complexes are molecules that form from the binding of multiple antigens to an antibody.⁵⁷ Although insoluble immune complexes are normally phagocytized by cells of the immune system, in cases of failed clearance or excess antigen-antibody presence, the immune complexes are deposited into tissues where they elicit a host of inflammatory responses.⁵⁷ Parallels in pathophysiology between MIS-C and KD, particularly vasculitis, have caused researchers to reconsider mechanisms of infectious agents and their crucial role in KD development, primarily through the

production of immune complexes. In MIS-C, investigators attribute the development of vasculitis to the obstruction of blood vessels with immune complexes. Through this process, immune complexes form through the interaction between viral spike proteins and anti-spike immunoglobulins; aggregates of immune complexes in vasculature lead to blood clotting, causing lesions in vascular tissue and subsequent inflammation.⁵⁸

Coronary vasculitis in KD presents with striking similarities to immune complex-induced systemic vasculitis in MIS-C by the SARS-CoV-2 viral spike protein. Such parallels have caused researchers to investigate the potential role of infections immune complexes, such as bacteria or viruses, that may be involved in the development of vasculitis in KD.

While discrepancies still remain about the precise causative agent behind circulating immune complexes in KD, current literature^{10, 59} confirms that immune complexes triggered by an etiological agent(s) play a distinct role in the pathogenesis of coronary vasculitis in KD and will be discussed later in this review.

2.4 The Gut Microbiome

Intestinal dysbiosis is defined as the changes of bacterial composition, metabolic activity, or distribution within the gut.⁶⁰ Such disturbances in the microbiota have been proposed to play essential roles in the pathophysiological processes of KD and MIS-C.

Differences in the microbiota composition have been detected in children with KD, including abnormal colonization by *Streptococcus* and *Ruminococcus* bacteria in acute and non-acute KD, respectively. The effects of such bacteria on the antigenic repertoire

of certain T cells and their pathological expansion has only recently been investigated. Suenaga et al.⁶¹ analyzed the potential of *Streptococcus*-produced superantigens in the pathogenesis of KD. Stool specimens obtained from 36 KD patients during the acute phase who were case matched with 26 healthy participants were found to have superantigen-related genes derived from *Streptococcus*. While the pathogenic role of superantigens has been discussed previously in this review, Suenaga et al.'s⁶¹ findings demonstrate a direct association between superantigens and superantigen-producing bacteria that might be associated with the onset of KD. The viral persistence of KD has been speculated to be a result of increased gut permeability due to zonulin – a protein discussed earlier in this review that is excreted by gut epithelial cells in response to dysbiosis of the microbiome. Zonulin disassembles tight junctions and allows viral antigens, such as those produced by *Streptococcus*, to escape into the blood stream and elicit an inflammatory immune response⁴⁶

There remains a paucity of literature investigating intestinal microbiota composition and its role, if any, in the observed symptoms of MIS-C. Recent literature has observed a decrease in *Faecalibacterium prasinii*, a bacterium commonly associated with inflammatory intestinal diseases such as irritable bowel syndrome and ulcerative colitis.⁵⁴ An increase in *Eggerthella lenta* was also detected in MIS-C patients and has been associated with Th17 cell activation and autoimmunity.⁵⁴ Despite uncertainty in gut microbial MIS-C drivers, loss of the gut mucosal barrier and intestinal dysbiosis have been established as key drivers in the pathophysiological process of MIS-C. Yonker et

al.⁶² found that a prolonged presence of SARS-CoV-2 in the gastrointestinal tract of children with MIS-C led to the release of zonulin and subsequent trafficking of SARS-CoV-2 antigens into the bloodstream. The zonulin-dependent loss of gut integrity that is all but absent in COVID-19-infected children suggests that the chronicity of SARS-CoV-2 dysbiosis in the gut directly influences mucosal barrier integrity in patients with MIS-C. Similarities between zonulin-dependent inflammatory pathways in MIS-C and KD highlight a potential therapeutic target that could be used to treat both diseases and will be discussed later in this review.

3. Etiology

The specific etiology of KD remains unclear. While earlier theories proposed a single pathological agent responsible for triggering the disease, current studies have rendered this hypothesis obsolete. At present, the development of KD is proposed to result from multiple agents infecting patients with a genetic predisposition associated with an abnormal immune system response.

While the origin(s) of KD remains undetermined, growing knowledge about the role of SARS-CoV-2 as an etiological agent of MIS-C, and its similarities to the exaggerated immune response via cytokine storm observed in KD, support potential of a viral antigen hypothesis. Such theories will be expanded upon in this section.

3.1 Etiological Theories of KD

Viral Agents

Detection of antibodies to multiple antigens in children with KD support a multi-antigen hypothesis. These include Epstein-Barr virus (EBV), human coronavirus, and retrovirus. EBV is a member of the herpes virus family. The role of EBV infection in the pathogenesis of KD remains elusive. In their serological study of EBV in 57 patients with KD, Kikuta et al.⁶³ reported that 86% of patients (n = 49) presented with evidence of EBV infection during the first month following onset of KD. Similar findings have been reported in various case studies.^{64, 65} Whether or not EBV acts as a concurrent or causative agent of KD, however, remains unclear. It has been demonstrated in vitro EBV can up-regulate the production of IL-6, an inflammatory cytokine that activates endothelial cells and platelets consistent with KD pathology. Contrarily, Fuse et al.⁶⁵ found that at the onset of KD, patients aged 1-6 years old had significantly lower EBV levels relative to patient controls. The authors speculated that EBV infection could play a defensive role in the onset of KD such that decreasing prevalence of EBV infection in certain populations may be responsible for the emergence of KD. Further investigation is required to discern the etiological role of EBV infection in KD.

A novel human coronavirus designated “New Haven coronavirus” (HCoVNH), has also been proposed as an etiological agent of KD. In their case-control study of 11 children with KD and 22 control subjects, Esper et al.⁶⁶ found that 73% of KD patients (n = 8) tested positive for HCoVNH, compared to only 4.5% (n = 1) of controls. While the full

clinical spectrum of symptoms caused by HCoVNH infection have not been fully characterized, the virus has been observed to cause respiratory tract infections consistent with KD. The authors propose that although KD is likely distinct from the viral respiratory tract infection directly caused by HCoVNH, abnormal clonal expansion of CD8+ T cells in response to the infectious agent, in combination with genetic predispositions of the host, may result in KD.

Prior literature has also investigated the retroviral etiology of KD. In their serological study, Shulman and Rowley⁶⁷ cultivated blood samples of 18 children with KD to examine reverse transcriptase (RT) activity. The authors identified RT activity on 8 of 18 children with KD, compared to only 1 of 18 controls, and suggested a casual relation between an undetermined retroviral agent and KD. Speculations of a retroviral etiology of KD have since been refuted, however, by studies such as Rowley et al.'s⁶⁸ which determined that polymerase activity of cultured cells from patients with KD were deoxyribonucleic acid (DNA)-dependent DNA polymerase rather than viral reverse transcriptase, an RNA-dependent DNA polymerase.

Bacterial Agents

A bacterial toxin causing KD has recently been a hypothesis favored by some investigators. The current theory posits that the GI tract – the largest lymphoid tissue in the body that is constantly exposed to a milieu of microorganisms – could serve as a host

for infectious microbiota.^{37, 69} In Nagata et al.'s³⁷ immunohistochemical analysis, biopsies performed on the mucous membrane of the duodenum of infants with KD revealed that certain antigens had likely invaded and significantly activated the host's immune system. The authors suspected that the potential KD-inducing antigens were of staphylococcal or streptococcal origin – superantigen-producing bacteria discussed previously in this review that cause inflammation through non-specific T cell activation. Current theories further support KD as a staphylococcal or streptococcal bacterial-mediated illnesses by highlighting clinical similarities, like peeling of the hands and feet, and strawberry tongue.^{70, 71}

Advancement in Immune Cell Profiling

Identification of the etiology or etiologies of KD sits at a current crossroads where past etiological records can be used to fuel new molecular analytic approaches. Such methods are highlighted in a recent molecular analysis by Burns et al.⁷² who performed immune profiling of patients with KD using breakthrough flow cytometry software and fluorescent-labeled antibodies. Such methods reveal changes in the fluorescent intensity of specified biomarkers during immune cell activation that ultimately help in understanding the phenotypic consequences of these pathways. In their analysis, Burns et al.⁷² found innate cell responses correlated with specific clinical phenotypes, while T cell responses were variable across the cohort. The authors propose these results support a multi-agent hypothesis of KD, such that different antigenic stimuli could activate different branches of the adaptive immune response in KD.

3.2 Viral Triggers as a Shared Etiology Between KD and MIS-C

It is understood that viral infection by SARS-CoV-2 plays a crucial role in the development of MIS-C. The SARS-CoV-2 virus is characterized by a spike (S) protein envelope which mediates binding and entry into the host cell. The S protein facilitates entry into the host cell through its subunit, which binds to angiotensin-converting enzyme 2 (ACE 2) receptor and subsequently replicates to release viral antigens throughout the body.⁷³ The vast clinical symptoms observed in MIS-C can be explained by the variable distribution of ACE 2 receptors throughout different tissues of the body, which are highly expressed on epithelial cells of the organs including the intestines, lungs, cardiomyocytes, and blood vessels.⁷³

SARS-CoV-2 expresses similar superantigenic behaviors to speculated KD-related coronaviruses, HCoV-NH, through which antigen-antibody complexes are formed and result in excessive activation of the immune system via cytokine storm.⁶⁶ A notable distinction of SARS-CoV-2, however, is its novel surface protein structure which facilitates stronger interactions with ACE 2 receptors on endothelial cells and, consequently, a greater efficacy in host cell invasion.⁷⁴ Such characteristics are consistent with more severe symptoms observed in patients with MIS-C relative to KD, including myocardial dysfunction, fever, and GI abnormalities.⁷⁵

3.3 Environmental Triggers

The seasonality of KD is well recognized but varies among countries. In the United Kingdom, Australia, and the United States, peak incidence occurs in winter in spring, while summer predominates in China and Korea. Contrarily, seasonal KD incidences are less discernible able in Japan.⁷⁶ Divergent data could be a result of more prominent seasonal weather conditions, such that regions with distinct weather markers – such as ambient temperatures and precipitation – exhibit recognizable incidence patterns.⁷⁶ Such theories could be explained by Bronstein et al.⁷⁶, who found that KD incidence in San Diego County in the United States was negatively associated with average monthly temperature and positively associated with average monthly precipitation. Whether or not seasonal conditions independently predispose to KD or rather influence risk of exposure by influencing etiological agents remains unclear; however, the lack of consistent seasonal associations among countries supports the latter hypothesis.

Environmental toxins as a cause of KD have been generally ruled out. This understanding is consistent with the non-recurrent nature of KD in the absence of an identification and purposeful removal of a toxin from the environment.⁷⁷⁻⁷⁹ Interestingly, recent literature has observed association with wind currents and KD. Rodó et al.⁸⁰ reported that wind currents originating in central Asia that traverse the north Pacific revealed consistent patterns with KD cases, primarily in Japan, Hawaii, and San Diego. The authors speculate potential of an etiological agent, such as a fungal toxin, that could be transmitted through the wind and cause KD. Further investigation of the role of wind-

born transmission and the identification of the precise etiological agent(s) of KD is required to verify these speculations.

Pandemic prevention measures in response to COVID-19 have helped uncover key insights into the epidemiological patterns, and resultant etiopathogenesis of KD and MIS-C alike. A nationwide observational study in South Korea of 53,000 KD patients between January 2010 to September 2020 found that number of KD cases decreased by nearly 40% following the implementation of COVID-19 prevention efforts in February 2020.⁸¹ Furthermore, the seasonality of KD in South Korea, often most prevalent in the winter, all but disappeared. Such findings not only challenge speculations of seasonal conditions impacting KD, but also strongly suggests that the etiology of KD is related to unidentified respiratory pathogens.⁷⁹

A summary of etiological agents and proposed pathogenic mechanisms of KD and MIS-C are summarized in **Figure 4**.

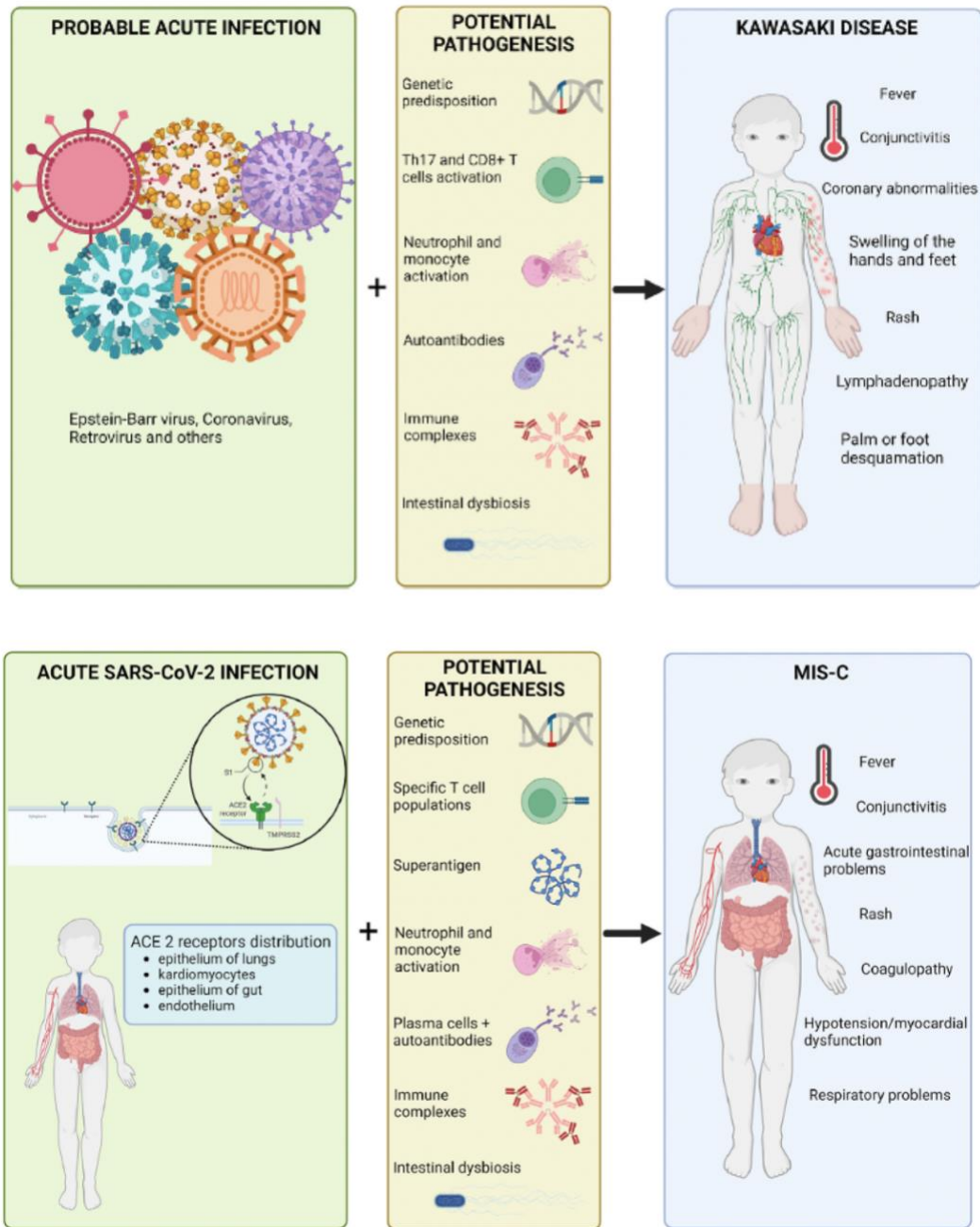


Figure 4. Proposed developmental pathways of Kawasaki Disease and Multisystem Inflammatory Syndrome in Children. (Top) Kawasaki disease (KD) is likely caused by multiple viral agents, most commonly including Epstein-Barr virus, Coronavirus, and Retrovirus. A combination of pathogen and host factors, including neutrophils, plasma

cells, autoantibodies, immune complexes, intestinal dysbiosis, and genetic predispositions, combined with an infectious agent likely contribute to the pathogenesis of KD. (Bottom) Multisystem Inflammatory Syndrome in Children (MIS-C) is likely a result of acute SARS-CoV-2 infection, characterized by a spike (S) protein envelope which facilitates viral entry into the host cell and binds to angiotensin-converting enzyme 2 (ACE 2) receptor – a ubiquitous receptor expressed on epithelial cells of organs throughout the body. Viral SARS-CoV-2 antigens are replicated and released throughout the body. A combination of pathogen and host factors, including neutrophils, plasma cells, autoantibodies, immune complexes, intestinal dysbiosis, and genetic predispositions, combined with SARS-CoV-2 infection contribute to the pathogenesis of MIS-C.

4. Epidemiology

4.1 Age and Gender as Evidence for an Infectious Cause

KD predominantly affects children from 6 months to 5 years old, with peak incidence occurring between 9-11 months of age.² A 2016 report by the Center for Disease Control reported that of 5440 KD-related hospitalizations, approximately 60% were of children under the age of 5.⁸² Such patterns can be explained by notable changes observed in the immune system corresponding to these ages. Rivas et al.¹⁶ highlights that children between 9-11 months old are of peak age for common childhood infections due to a significant decrease in passive maternal antibodies. The authors posit there may be protective maternal passive immunity against the causative agent of KD from birth to 6 months, and key elements of immune system maturation that occur in children at or beyond 6 years of age. Males are affected 2/3 more frequently than females, a feature observed in many infectious diseases due to sex differences in immune response that mediate susceptibility.⁸³

Due to the recency of the COVID-19 pandemic, the epidemiological nature of SARS-CoV-2 in children continues to be investigated. A recent meta-analysis by Jiang et al.⁸⁴ found that the mean age of MIS-C patients was 8.3 years of age (range 1.6 to 20 years), over half of which (58%) were males. While few adult cases of MIS related to SARS-CoV-2 (MIS-A) have been reported⁸⁵, it remains unclear why the virus predominantly affects school-aged children. Current literature has speculated that children's immune systems are uniquely able to suppress the initial SARS-CoV-2 infection, and then develop MIS-C.⁸⁶ Although age has not been determined as a characteristic diagnostic factor of MIS-C, observed age differences can nonetheless help to differentiate between the disease from KD.

4.2 Ethnicity as Evidence for Genetic Determinants

It is imperative to consider genetic predispositions associated with abnormal immune system responses that are speculated to be involved in the development of both KD and MIS-C.

The epidemiological characteristics of KD are well-documented and provide valuable insight into its etiology.¹⁷ Cases of KD have been reported worldwide, with incidences reported 10-30 times higher in Asian than Western countries, including Japan, Korean, China, and Taiwan.⁷⁹ Between 2017-2019, studies found that the occurrence of KD in children less than 5 years of age was roughly 359 per every 100,000 children in Japan, 202 in Korea, and only 19 in the United States.⁸⁷ Whether or not the observed patterns are

a result environmental or genetic factors, or a combination of both, has been under scrutiny. Rhim et al.¹⁷ highlights the time periods of the first reported cases of KD, an overwhelming number of which occurred between the 1960s – 1990s in Northeast Asian countries during notable periods of economic growth and westernization. However, these claims have been refuted by Dean et al.⁷⁸ in their epidemiology study who observed that Asian children living in the United States had the same high incidence rates of those living in Asia. Such observations reinforce hypotheses of a genetic role, rather than a cultural or geographic mediator, the predispose Asian children to KD. Race-specific incidence rates of KD have also been observed to be higher in Black children. In their 4.5-year statewide case study, Davis et al.⁸⁸ found that rates of KD among Black children in Washington state occurred in 23.4 per 100,000 children, nearly double the incidence of KD observed in White children. The authors posit that controlling for location (i.e. all patients living in the same state) could suggest that a difference in immune response could be due to genetics, although cultural and environmental factors could not be ruled out. Additional studies have also shown that African ancestry predicts heightened inflammatory response to pathogens, which could have a genetic basis that may have broad implications for the association with KD.⁸⁹

Current studies have also investigated the association of ethnicity with MIS-C. In 2020, the CDC determined that of 1097 cases of MIS-C, 75% of patients were Hispanic or African American.⁹⁰ These findings were further corroborated by Middleburg et al.⁹¹ in a multi-institutional case-control study of 73 MIS-C patients, who observed that children

with Black and Asian genetic backgrounds were 15 and 11 times, respectively, more likely than White children to develop COVID-19 related MIS-C. The authors refuted the idea that these disproportionate findings – particularly among Black children – could be entirely, if at all, accounted for by socioeconomic status, challenging that the observed prevalence of MIS-C is five times higher than the overrepresentation of Black American adults diagnosed with COVID-19. The overrepresentation among adults has been largely linked to existing health disparities. If the overrepresentation of MIS-C in Black children was due to the same disparities, Middleburg et al.⁹¹ argues a similar prevalence pattern would be observed. Such discrepancies could suggest evidence of a genetic predisposition.

Trends in ethnicity and disease prevalence between KD and MIS-C warrant further discussion, particularly in Black children. As reviewed previously, incidence of KD in Black children has been estimated to be two times higher compared with White children. Similar incidence patterns observed among Black children diagnosed with MIS-C could suggest the possibility of a shared genetic predisposition between the two diseases that influences similar hyperinflammatory response pathways. While a similar, though weaker, association was observed among Asian children and MIS-C in Middleburg et al.'s⁹¹ findings, such results should be considered with caution. The author's included patients diagnosed with MIS-C based on clinical evaluation. Such methods increase the likelihood of incorrectly including cases unrelated to SARS-CoV-2 infection that present with similar symptomology, such a KD. The observed association could therefore be an

overestimate and partially due to KD, which is known to have a strong association with Asian children. Further studies should aim to elucidate the potential of genetic predispositions toward hyperinflammatory responses and their association with ethnicity, particularly among Black and Asian children.

THERAPEUTIC STRATEGIES & OUTCOMES

1. Intravenous Immunoglobulin Therapy

Intravenous immunoglobulin (IVIG) therapy is standard first-line treatment for KD, and has proved successful in the management of MIS-C. Therapeutic IVIG consists of normal IgG – a high-affinity antibody that controls toxins, viruses, and bacteria through neutralization, phagocytic, and complement mechanisms – obtained from the plasma of healthy blood donors that is administered to patients. IVIG modulates immune pathways through a complex mechanism of synergistic events that ultimately normalize a compromised immune system.⁹² These processes include regulating the activation of B and T lymphocytes, neutralization of pathogenic autoantibodies, interference with antigen presenting cells, and interaction with cytokines and endothelial cells that provoke anti-inflammatory pathways.⁹³ A summary of the mechanisms of action of IVIG are summarized in **Figure 5**.

Interaction with Lymphocytes

IVIG has been reported to decrease Th17 cell proliferation and increase Treg cell proliferation. As discussed previously in this review, Th17 cells lead to the production of pro-inflammatory cytokines including IL-17, IL-6, and TNF, all of which are observed at increased levels in both KD and MIS-C. Inhibition of Th17 cell proliferation is modulated by IgG's fragment antigen-binding (Fab) region, which binds to Th17 cell receptors and blocks transcriptional pathways necessary for replication.⁹³

Alternatively, anti-inflammatory T_{reg} cells, which are observed at lower-than-normal levels in KD patients, also expand in response to IVIG therapy. This novel immune regulatory function of IgG has recently been described by Hsieh et al.³⁶, through which T_{reg} cells recognize the heavy chain constant region (fragment crystallizable region, Fc) of IgG presented by dendritic cells, and stimulate expansion.

Interaction with Autoantibodies

Interaction between IVIG and variable regions of autoantibodies provides a basis for their ability to regulate autoreactive B cells (sources of autoantibodies). IVIG has been observed to neutralize autoantibodies and/or inhibit their binding to autoantigens, thereby dysregulating the pathway through which autoantigens are presented to T cells and induce hyperinflammatory responses.⁹⁴ While speculation of autoantibodies towards AECAs and endoglin have been discussed earlier in this review, there is currently no consistent evidence of a direct pathogenic role for autoantibodies in KD or MIS-C. As such, IVIG regulatory mechanisms of autoantibodies in these diseases remains merely postulated and further research is required to verify its therapeutic role.

Interaction with Antigen Presenting Cells

Dendritic cells (DCs) are among the most ubiquitous antigen presenting cells that take up antigens to interact with and stimulate T lymphocytes. It has been observed that IVIG can mediate DC expansion to induce anti-inflammatory T_{reg} cell proliferation. IVIG expands T_{reg} cells via induction of cyclooxygenase-2- dependent prostaglandin E2 (PGE2), which

are hormone-like lipids that increase migration of DCs under pathological conditions. Maintaining normal motility of DCs is crucial for migration to the lymph nodes and subsequent stimulation of T_{reg} cells.⁹⁵

Interaction with Complement System

The complement system is considered the body's front line of defense against pathogens and acts to induce a series of innate inflammatory responses.⁹³ Among these responses include complement-induced neutrophil activation, which leads to an early neutrophilic surge in KD and MIS-C as discussed earlier in this review. IVIGs contain antibodies against a particular lectin protein – sialic acid-binding Ig-like lectin (Siglec) – that resides on the surface of neutrophils. The anti-Siglec antibodies present in IVIG interact with surface Siglec proteins, resulting in neutrophil death and subsequent anti-inflammatory effects.⁹⁶

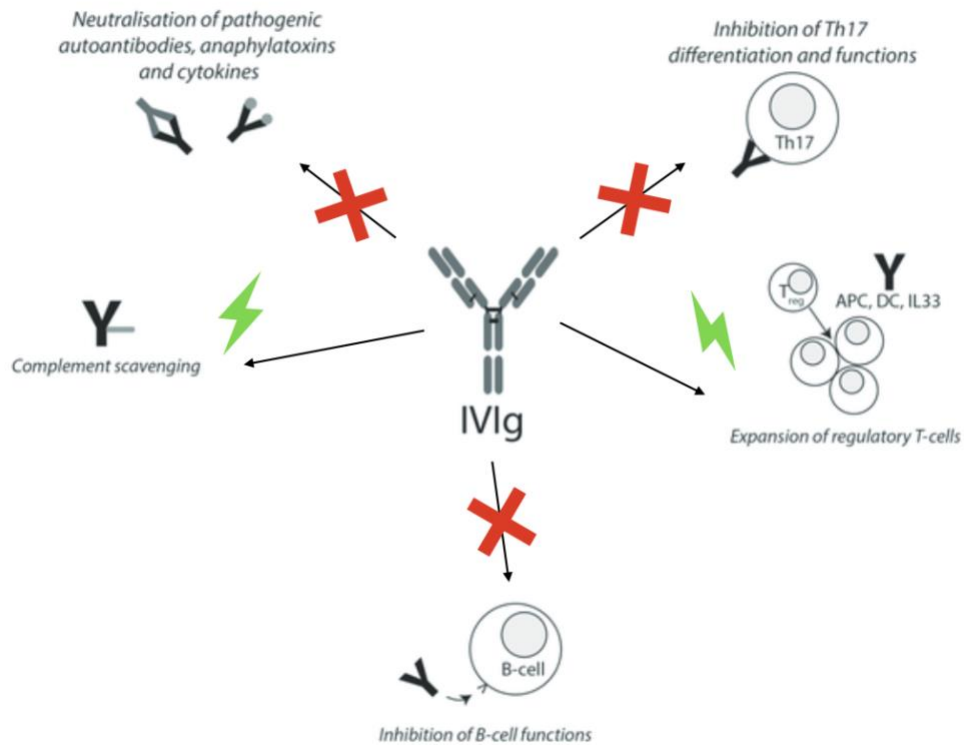


Figure 5. Therapeutic mechanisms of intravenous immunoglobulin. Intravenous immunoglobulin modulates immune pathways through a complex mechanism of synergistic events that ultimately normalize a compromised immune system. These processes include (clockwise, from bottom) inhibition of B cell activation, regulation of the host's complement system, neutralization of pathogenic autoantibodies, inhibition of Th17 cell proliferation, increasing T_{reg} cell proliferation and interference with antigen presenting cells. Figure adapted from Hoffman and Enk.⁹⁷

Clinical Outcomes on KD and MIS-C

IVIg therapy has emerged as the standard of care for management of KD and can alleviate symptoms within hours of initiating infusion. While the primary goal of IVIG administration in KD is to prevent coronary artery damage and systemic vascular inflammation, it also eradicates concurrent symptoms including fever, rash, edema, and conjunctival hyperemia.⁹³ In their recent meta-analysis including 4,609 KD patients

comparing high-dose IVIG regimens to medium- and low-dose regimens and acetylsalicylic acid (aspirin), Broderick et al.⁹⁸ found that patients receiving high-dose IVIG regimens (> 1.6 g/kg) experienced reduced incidence of CAAs compared to medium ($1.6 - 1.0$ g/kg) - and low-dose (< 1.0 g/kg) regimens, as well as reduced duration of fever, and need for additional treatment. Such findings suggest that response to IVIG occurs in a dose-dependent manner, and that high-dose IVIG regimens are not only safe, but also the most effective in KD treatment. Standard initial pharmacological management currently involves IVIG at a single 12-hour infusion at a dose of 2 g/kg, supplemented by 30 to 50 mg of aspirin. This regimen has been shown to reduce long-term coronary injury from 25% to 4.7%.⁹⁹

While the use of IVIG in the treatment of KD has been well-established, its efficacy in MIS-C remains under investigation. In their literature review, Sharma et al.² found that 70-100% of patients ($n=1,020$) were treated with IVIG as a first-line agent, with satisfactory results. These findings were further validated by Feldstein et al.⁸ in their targeted surveillance of 186 MIS-C patients, who found that IVIG was generally preferred (77% of patients) to mitigate hyperinflammatory symptoms. Alternatively, some studies have found IVIG to be ineffective in 51%-81% of MIS-C patients. In their retrospective cohort study of 19 patients with MIS-C, Vukomanovic et al.²⁵ found that 70% of patients were unresponsive to IVIG. Such findings further emphasize pathological distinctions between MIS-C and KD and support the notion that MIS-C

presents with more profound inflammation that may require alternative therapeutics to mitigate immune dysregulation.

2. Alternative Treatment Strategies

Despite the well documented efficacy of IVIG in the treatment of KD and its promising therapeutic role in MIS-C, patients do not always respond to this regimen. In fact, Rambabu et al.¹⁰⁰ has identified key metabolic pathways that may contribute to IVIG resistance, including increased expression of inflammatory genes, abnormal regulation of Th17 response, and high mitochondrial activity. Clinical risk factors have also been proposed as identifiers for IVIG resistance, including coronary artery dilation, age < 6 month, and Asian race.¹⁰¹ Such findings could assist in early identification of IVIG non-responders and the implementation of alternative therapies.

Recent discoveries involving alternative therapeutic approaches and outcomes, combined with increasing knowledge of IVIG resistance, have not only advanced management of KD and MIS-C but also further shed light on important mechanistic differences in their inflammatory pathways. A select number of these interventions include corticosteroids, zonulin antagonists, and cytokine antagonists.

2.1 Corticosteroids

Corticosteroid treatment is utilized in a broad range of vasculitis diseases with great efficacy. Although its role in each disease is somewhat pathway-specific, corticosteroids generally function to suppress the transcription of inflammatory proteins. In KD, the use

of corticosteroids as part of an initial treatment or second-line treatment has been observed as a promising therapeutic approach. In their pooled meta-analysis of 922 KD participants treated with corticosteroids, Wardle et al.¹⁰² found that patients experienced improved coronary artery abnormalities, decreased hospital stay and duration of clinical symptoms. Mechanism of corticosteroid efficacy in KD is understood to be due to the suppression of inflammatory neutrophils which damage arterial tissue and subsequently induce aneurysm, as discussed previously in this review. Interestingly, in a subgroup analysis the authors found that certain patient cohorts, including those based in Asia, with higher risk scores, and receiving longer treatment may experience greater benefits from steroid treatment. Additional large-scale cohort analyses are required to further investigate these questions.

Due to the robust inflammatory nature of MIS-C, IVIG alone may not be sufficient in all cases and may require use of more comprehensive immunosuppressants like corticosteroids as first-line therapy. In their case study of 29 MIS-C patients treated with IVIG alone, Felsenstein et al.⁶ found that 32% of patients treated went into remission and required additional treatment with corticosteroids. Vukomanovic et al.¹⁰³ goes even further to suggest that corticosteroid intervention alone may be more effective than IVIG, observing that patients treated with only IVIG had an almost 19-fold higher probability of treatment failure than those treated with corticosteroids. An observed elevation of IL-6 in these patients increased vascular permeability and subsequent myocarditis. Such findings

support the notion that MIS-C inflammation is much more robust than KD and may require alternative or supplemental therapeutic intervention.

2.2 Zonulin Antagonists

The role of zonulin-dependent increase in gut permeability in KD and MIS-C patients has been under recent investigation as a potential therapeutic target for patients who are unresponsive to ant-inflammatory therapies like IVIG. As proof of concept, Rivas et al.¹⁶ observed that pharmacological blockade of zonulin in KD-induced mice significantly reduced intestinal permeability, cardiovascular inflammation, and abdominal aorta dilation. Zonulin blocking pathways also halted the development of cardiovascular lesions associated with KD. The authors also observed a significant decrease in circulating levels and deposition of IgA – a recently detected hallmark of KD that appears to infiltrate tissues upon infectious exposure.

Similar mechanisms have also proven effective in MIS-C patients. In their comparative cohort study, Yonker et al.⁶² administered larazotide, a zonulin antagonist, to four MIS-C children in addition to steroids and IVIG. The authors compared outcomes from this cohort to MIS-C patients who underwent steroid and IVIG treatment only and observed that children who received larazotide experienced significantly faster resolution of GI symptoms, drop in SARS-CoV-2 plasma antigen levels, and shorter hospital stays.

Similar findings between these studies further confirm the shared zonulin-dependent mechanisms of inflammation between KD and MIS-C, as well as demonstrate the potential benefit of hybrid therapies that can be implemented with IVIG.

2.3 Cytokine Antagonists

Growing knowledge on the role of distinct cytokines in the pathogenesis of KD and MIS-C have offered insight into potential therapeutic targets. As discussed earlier in this review, TNF α and IL-1 are potent pro-inflammatory cytokines that are observed at elevated levels in patients with KD and MIS-C, and therefore serve as appealing potential therapeutic targets. Infliximab, a TNF α -blocker, has been used as second-line therapy in KD and MIS-C patients with IVIG resistance and persistent inflammation.²² Early intervention with infliximab has been proven to induce a rapid inflammatory resolution and improved outcomes in patients with both diseases.^{22, 104} Similar results have been observed using IL-1 antagonist, anakinra, in patients refractory to IVIG and corticosteroids.¹⁰⁵

While there remains no clear consensus on precise second-line treatment interventions, literature suggests that anakinra is favored in MIS-C, whereas infliximab may be more often deployed in KD.¹⁰⁶ Although its mechanistic advantage in MIS-C is not completely clear, Hadjadj et al.¹⁰⁷ showed that in adult patients with severe COVID-19, IL-1 plays a critical role in the pathogenesis of excessive inflammation. As such, IL-1 receptor antagonists such as anakinra may prove more advantageous in COVID-19-related MIS-C

in down-regulating downstream proinflammatory cascades secondary to IL-1. These findings further highlight potential pathogenic differences between MIS-C and KD that warrant consideration, particularly in the optimization of therapeutic intervention.

CONCLUSION

Clinical, pathological, etiological, and epidemiological differences indicate that although KD and MIS-C present with certain phenotypic similarities (fever, mucocutaneous disturbances, cardiac dysfunction, and skin rashes), they are two distinct diseases.

Clinical hallmarks of KD include acute vasculitis and development of CAAs, however growing diagnostic strategies have reduced incidence of CAA-related complications to <10%. Cardiac involvement in MIS-C is more prevalent, with higher incidence of CAA-related complications, myocarditis, and cardiogenic shock. Children with MIS-C generally present with more prominent respiratory, GI, and neurological abnormalities as well .

The pathophysiology of KD and MIS-C are both associated with intense activation of innate and adaptive immune system responses and subsequent cytokine storm resulting in systemic inflammation. Genetic predispositions, particularly SNPs in genes related to T and B cell activation (CASP3, ITPKC, and BLK) and cardiac remodeling (TGF- β) have been detected in patients with KD. Similar expression of ViP signature genes as well as KD-specific transcript diagnostic signature have been detected in both diseases and suggest a shared proximal pathway of immunopathogenesis. Evidence of a superantigen-mediated disease is more likely in MIS-C, through which the SARS-CoV-2 viral S protein may behave like a superantigen, triggering a cytokine storm that results in the development of cardiogenic shock. Both KD and MIS-C are associated with high levels

of neutrophils and NETs, IL-17, and IL-6 inflammatory cytokines. However, MIS-C is characterized by pronounced lymphopenia, particularly circulating CD4⁺ T cells. Current literature suggests reduced lymphocytes are a result of either T cell shuttling to inflamed tissues or the compromising of T cell response via superantigen mechanisms. A growing body of literature has also detected concentrations of an antigen-specific IgA derived from activated B cells in host tissues of both diseases. These findings notably support etiological theories of KD as an antigen-driven disease. Presence of AECAs is unique to KD and suggest that autoantibodies likely play a pathogenic role in vasculitis symptoms. Immune complexes formed through antigen-antibody excess have been detected in both diseases, and explain parallels observed in tissue pathology. Intestinal dysbiosis involving *Streptococcus* and SARS-CoV-2 have been observed in KD and MIS-C, respectively, and are speculated to escape into the bloodstream via zonulin-dependent loss of gut integrity and elicit persistent inflammation.

It is likely that a combination of pathogen and host factors contribute to the origin of both KD and MIS-C. Positive SARS-CoV-2 serology in MIS-C patients indicates a link to prior infection or exposure, while advancements in immune cell profiling indicate that KD is a result of multiple viral agents which activate different branches of the immune system. Potential host factors include age, gender, genetic, and epigenetic predispositions. KD predominantly affects children <5 years old, while MIS-C has been reported in a wide age range with a mean age of 8 years. Infection among males is more common in both diseases. Interestingly, MIS-C is reportedly more common among

children of African American or Hispanic descent – a stark contrast to the high frequencies of East Asian populations diagnosed with KD.

IVIg remains the standard of care for KD and has proven efficacious in MIS-C treatment, but to a lesser degree. Differences in host response to IVIg treatment are likely a result of the heightened inflammatory symptoms in MIS-C and further emphasize key immunologic differences that classify the two as essentially distinct diseases. Alternative therapeutic interventions include corticosteroids, zonulin and cytokine antagonists.

In conclusion, several clinical features overlap between KD and MIS-C and indicate they may belong under the same umbrella of inflammatory disorders. However, key differences in clinical, pathological, etiological, and epidemiological observations enhance our understanding of these diseases as two distinct entities. Despite recent advancements in knowledge of MIS-C, and its contribution to our ongoing understanding of KD, critical gaps remain. Additional long-term research of KD and MIS-C investigating etiologic agents and immunopathogenic mechanisms is required to better understand at-risk populations and inform diagnostic and therapeutic approaches.

BIBLIOGRAPHY

1. Wessels PA, Bingler MA. A comparison of Kawasaki Disease and multisystem inflammatory syndrome in children. *Progress in Pediatric Cardiology*. Jun 2022;65:101516. doi:10.1016/j.ppedcard.2022.101516
2. Sharma C, Ganigara M, Galeotti C, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. *Nature Reviews Rheumatology*. Dec 2021;17(12):731-748. doi:10.1038/s41584-021-00709-9
3. Son MB, Gauvreau K, Ma L, et al. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics*. Jul 2009;124(1):1-8. doi:10.1542/peds.2008-0730
4. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. *Journal of Clinical Investigation Insight*. Jun 4 2020;5(11)doi:10.1172/jci.insight.138999
5. Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. Sep 3 2020;136(10):1169-1179. doi:10.1182/blood.2020007008
6. 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. *The Journal of the American Medical Association*. Mar 16 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091
7. Gaitonde M, Ziebell D, Kelleman MS, et al. COVID-19-Related Multisystem Inflammatory Syndrome in Children Affects Left Ventricular Function and Global Strain Compared with Kawasaki Disease. *Journal of the American Society of Echocardiography*. Oct 2020;33(10):1285-1287. doi:10.1016/j.echo.2020.07.019
8. Felsenstein S, Willis E, Lythgoe H, et al. Presentation, Treatment Response and Short-Term Outcomes in Paediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). *Journal of Clinical Medicine*. Oct 14 2020;9(10)doi:10.3390/jcm9103293
9. Ghosh P, Katkar GD, Shimizu C, et al. Publisher Correction: An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. *Nature Communications*. Aug 11 2022;13(1):4729. doi:10.1038/s41467-022-32479-7
10. Singh S, Gupta A, Jindal AK, et al. Pulmonary presentation of Kawasaki disease- A diagnostic challenge. *Pediatric Pulmonology*. Jan 2018;53(1):103-107. doi:10.1002/ppul.23885

11. Khoury L, Livnat G, Hamad Saied M, Yaacoby-Bianu K. Pneumonia in the presentation of Kawasaki disease: The syndrome or a sequence of two diseases? *Clinical Case Reports*. Dec 2022;10(12):e6676. doi:10.1002/ccr3.6676
12. Camporesi A, Gemma M, Buonsenso D, et al. Lung Ultrasound Patterns in Multisystem Inflammatory Syndrome in Children (MIS-C)-Characteristics and Prognostic Value. *Children (Basel)*. Jun 21 2022;9(7)doi:10.3390/children9070931
13. Zhang QY, Xu BW, Du JB. Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. *World Journal of Pediatrics*. Aug 2021;17(4):335-340. doi:10.1007/s12519-021-00435-y
14. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *The New England Journal of Medicine*. Jul 23 2020;383(4):334-346. doi:10.1056/NEJMoa2021680
15. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal Symptoms as a Major Presentation Component of a Novel Multisystem Inflammatory Syndrome in Children That Is Related to Coronavirus Disease 2019: A Single Center Experience of 44 Cases. *Gastroenterology*. Oct 2020;159(4):1571-1574.e2. doi:10.1053/j.gastro.2020.05.079
16. Noval Rivas M, Arditi M. Kawasaki Disease and Multisystem Inflammatory Syndrome in Children: Common Inflammatory Pathways of Two Distinct Diseases. *Rheumatic Disease Clinics of North America*. Aug 2023;49(3):647-659. doi:10.1016/j.rdc.2023.03.002
17. Rhim JW, Kang JH, Lee KY. Etiological and pathophysiological enigmas of severe coronavirus disease 2019, multisystem inflammatory syndrome in children, and Kawasaki disease. *Clinical and Experimental Pediatrics*. Apr 2022;65(4):153-166. doi:10.3345/cep.2021.01270
18. Kwak JH, Lee SY, Choi JW. Clinical features, diagnosis, and outcomes of multisystem inflammatory syndrome in children associated with coronavirus disease 2019. *Clinical and Experimental Pediatrics*. Feb 2021;64(2):68-75. doi:10.3345/cep.2020.01900
19. Chen TH. Neurological involvement associated with COVID-19 infection in children. *Journal of Neurological Sciences*. Nov 15 2020;418:117096. doi:10.1016/j.jns.2020.117096

20. Lin CH, Lai JN, Lee IC, et al. Association Between Kawasaki Disease and Childhood Epilepsy: A Nationwide Cohort Study in Taiwan. *Frontiers in Neurology*. 2021;12:627712. doi:10.3389/fneur.2021.627712
21. Bova SM, Serafini L, Capetti P, et al. Neurological Involvement in Multisystem Inflammatory Syndrome in Children: Clinical, Electroencephalographic and Magnetic Resonance Imaging Peculiarities and Therapeutic Implications. An Italian Single-Center Experience. *Frontiers in Pediatrics*. 2022;10:932208. doi:10.3389/fped.2022.932208
22. Tremoulet AH, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet*. May 17 2014;383(9930):1731-8. doi:10.1016/s0140-6736(13)62298-9
23. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. *Arthritis & Rheumatology*. Apr 2022;74(4):e1-e20. doi:10.1002/art.42062
24. Rowley AH, Baker SC, Orenstein JM, Shulman ST. Searching for the cause of Kawasaki disease--cytoplasmic inclusion bodies provide new insight. *Nature Reviews Microbiology*. May 2008;6(5):394-401. doi:10.1038/nrmicro1853
25. Vaňková L, Bufka J, Křížková V. Pathophysiological and clinical point of view on Kawasaki disease and MIS-C. *Pediatric & Neonatology*. Sep 2023;64(5):495-504. doi:10.1016/j.pedneo.2023.05.002
26. Lin J, Harahsheh AS, Raghuvver G, et al. Emerging Insights Into the Pathophysiology of Multisystem Inflammatory Syndrome Associated With COVID-19 in Children. *Canadian Journal of Cardiology*. Jun 2023;39(6):793-802. doi:10.1016/j.cjca.2023.01.002
27. Onouchi Y, Fukazawa R, Yamamura K, et al. Variations in ORAI1 Gene Associated with Kawasaki Disease. *PLoS One*. 2016;11(1):e0145486. doi:10.1371/journal.pone.0145486
28. Onouchi Y. Molecular genetics of Kawasaki disease. *Pediatric Research*. May 2009;65(5 Pt 2):46r-54r. doi:10.1203/PDR.0b013e31819dba60
29. Kim JJ, Hong YM, Yun SW, et al. Identification of B-cell-related HSPG2 and CDSN as susceptibility loci for Kawasaki disease. *Human Immunology*. Oct 2023;84(10):567-570. doi:10.1016/j.humimm.2023.07.001

30. Shimizu C, Jain S, Davila S, et al. Transforming growth factor-beta signaling pathway in patients with Kawasaki disease. *Circulation: Cardiovascular Genetics*. Feb 2011;4(1):16-25. doi:10.1161/circgenetics.110.940858
31. Bartram U, Molin DG, Wisse LJ, et al. Double-outlet right ventricle and overriding tricuspid valve reflect disturbances of looping, myocardialization, endocardial cushion differentiation, and apoptosis in TGF-beta(2)-knockout mice. *Circulation*. Jun 5 2001;103(22):2745-52. doi:10.1161/01.cir.103.22.2745
32. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *New England Journal of Medicine*. Aug 24 2006;355(8):788-98. doi:10.1056/NEJMoa055695
33. Tone Y, Furuuchi K, Kojima Y, Tykocinski ML, Greene MI, Tone M. Smad3 and NFAT cooperate to induce Foxp3 expression through its enhancer. *Nature Immunology*. Feb 2008;9(2):194-202. doi:10.1038/ni1549
34. Fleischer B. Superantigens. *Apmis*. Jan 1994;102(1):3-12. doi:10.1111/j.1699-0463.1994.tb04839.x
35. Macias ES, Pereira FA, Rietkerk W, Safai B. Superantigens in dermatology. *Journal of the American Academy of Dermatology*. Mar 2011;64(3):455-72; quiz 473-4. doi:10.1016/j.jaad.2010.03.044
36. Hsieh LE, Song J, Tremoulet AH, Burns JC, Franco A. Intravenous immunoglobulin induces IgG internalization by tolerogenic myeloid dendritic cells that secrete IL-10 and expand Fc-specific regulatory T cells. *Clinical and Experimental Immunology*. Jun 23 2022;208(3):361-371. doi:10.1093/cei/uxac046
37. Nagata S, Yamashiro Y, Ohtsuka Y, et al. Heat shock proteins and superantigenic properties of bacteria from the gastrointestinal tract of patients with Kawasaki disease. *Immunology*. Dec 2009;128(4):511-20. doi:10.1111/j.1365-2567.2009.03135.x
38. Mancina L, Wahlström J, Schiller B, et al. Characterization of the T-cell receptor V-beta repertoire in Kawasaki disease. *Scandinavian Journal of Immunology*. Oct 1998;48(4):443-9. doi:10.1046/j.1365-3083.1998.00415.x
39. Jun JS, Jung YK, Lee DW. Relationship between vitamin D levels and intravenous immunoglobulin resistance in Kawasaki disease. *Korean Journal of Pediatrics*. Jul 2017;60(7):216-220. doi:10.3345/kjp.2017.60.7.216
40. Fuchs TA, Abed U, Goosmann C, et al. Novel cell death program leads to neutrophil extracellular traps. *Journal of Cell Biology*. Jan 15 2007;176(2):231-41. doi:10.1083/jcb.200606027

41. Yamashita K, Takaori-Kondo A, Mizugishi K. Exaggerated neutrophil extracellular trap formation in Kawasaki disease: a key phenomenon behind the outbreak in western countries? *Annals of Rheumatic Diseases*. Aug 21 2020;doi:10.1136/annrheumdis-2020-218593
42. Mutua V, Gershwin LJ. A Review of Neutrophil Extracellular Traps (NETs) in Disease: Potential Anti-NETs Therapeutics. *Clinical Reviews in Allergy & Immunology*. Oct 2021;61(2):194-211. doi:10.1007/s12016-020-08804-7
43. Boribong BP, LaSalle TJ, Bartsch YC, et al. Neutrophil profiles of pediatric COVID-19 and multisystem inflammatory syndrome in children. *Cell Reports Medicine*. Dec 20 2022;3(12):100848. doi:10.1016/j.xcrm.2022.100848
44. 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. *The Lancet Child & Adolescent Health*. Oct 2020;4(10):790-794. doi:10.1016/s2352-4642(20)30257-1
45. 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. *EClinicalMedicine*. May 2021;35:100850. doi:10.1016/j.eclinm.2021.100850
46. El Asmar R, Panigrahi P, Bamford P, et al. Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure. *Gastroenterology*. Nov 2002;123(5):1607-15. doi:10.1053/gast.2002.36578
47. Guo MM, Tseng WN, Ko CH, Pan HM, Hsieh KS, Kuo HC. Th17- and Treg-related cytokine and mRNA expression are associated with acute and resolving Kawasaki disease. *Allergy*. Mar 2015;70(3):310-8. doi:10.1111/all.12558
48. 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. *Science Immunology*. Mar 2 2021;6(57)doi:10.1126/sciimmunol.abf7570
49. Gelzo M, Castaldo A, Giannattasio A, et al. MIS-C: A COVID-19-associated condition between hypoimmunity and hyperimmunity. *Frontiers in Immunology*. 2022;13:985433. doi:10.3389/fimmu.2022.985433
50. Rowley AH, Shulman ST, Mask CA, et al. IgA plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute Kawasaki disease. *Journal of Infectious Disease*. Oct 2000;182(4):1183-91. doi:10.1086/315832

51. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. *Journal of Immunology*. Jan 15 2001;166(2):1334-43. doi:10.4049/jimmunol.166.2.1334
52. Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nature Medicine*. Nov 2020;26(11):1701-1707. doi:10.1038/s41591-020-1054-6
53. Thiriard A, Meyer B, Eberhardt CS, et al. Antibody response in children with multisystem inflammatory syndrome related to COVID-19 (MIS-C) compared to children with uncomplicated COVID-19. *Frontiers in Immunology*. 2023;14:1107156. doi:10.3389/fimmu.2023.1107156
54. Suskun C, Kilic O, Yilmaz Ciftdogan D, et al. Intestinal microbiota composition of children with infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and multisystem inflammatory syndrome (MIS-C). *European Journal of Pediatrics*. Aug 2022;181(8):3175-3191. doi:10.1007/s00431-022-04494-9
55. Consiglio CR, Cotugno N, Sardh F, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell*. Nov 12 2020;183(4):968-981.e7. doi:10.1016/j.cell.2020.09.016
56. Sakurai Y. Autoimmune Aspects of Kawasaki Disease. *Journal of Investigational Allergology and Clinical Immunology*. 2019;29(4):251-261. doi:10.18176/jiaci.0300
57. Philip S, Jindal A, Krishna Kumar R. An update on understanding the pathophysiology in Kawasaki disease: Possible role of immune complexes in coronary artery lesion revisited. *International Journal of Rheumatic Diseases*. Aug 2023;26(8):1453-1463. doi:10.1111/1756-185x.14816
58. Bukulmez H. Current Understanding of Multisystem Inflammatory Syndrome (MIS-C) Following COVID-19 and Its Distinction from Kawasaki Disease. *Current Rheumatology Reports*. Jul 3 2021;23(8):58. doi:10.1007/s11926-021-01028-4
59. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2007-2008 nationwide survey. *American Journal of Epidemiology*. 2010;20(4):302-7. doi:10.2188/jea.je20090180
60. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. Mar 27 2014;157(1):121-41. doi:10.1016/j.cell.2014.03.011
61. Suenaga T, Suzuki H, Shibuta S, Takeuchi T, Yoshikawa N. Detection of multiple superantigen genes in stools of patients with Kawasaki disease. *Journal of Pediatrics*. Aug 2009;155(2):266-70. doi:10.1016/j.jpeds.2009.03.013

62. Yonker LM, Gilboa T, Ogata AF, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *Journal of Clinical Investigation*. Jul 15 2021;131(14)doi:10.1172/jci149633
63. Kikuta H, Matsumoto S, Osato T. Kawasaki disease and Epstein-Barr virus. *Acta Paediatrica*. Dec 1991;33(6):765-70. doi:10.1111/j.1442-200x.1991.tb02606.x
64. Kikuta H, Nakanishi M, Ishikawa N, Konno M, Matsumoto S. Detection of Epstein-Barr virus sequences in patients with Kawasaki disease by means of the polymerase chain reaction. *Intervirology*. 1992;33(1):1-5. doi:10.1159/000150224
65. Fuse S, Fujinaga E, Mori T, Hotsubo T, Kuroiwa Y, Morii M. Children with Kawasaki disease are not infected with Epstein-Barr virus. *The Pediatric Infectious Disease Journal*. Mar 2010;29(3):286-7. doi:10.1097/INF.0b013e3181c3f111
66. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *Journal of Infectious Disease*. Feb 15 2005;191(4):499-502. doi:10.1086/428291
67. Shulman ST, Rowley AH. Does Kawasaki disease have a retroviral aetiology? *Lancet*. Sep 6 1986;2(8506):545-6. doi:10.1016/s0140-6736(86)90115-7
68. Rowley A, Castro B, Levy J, et al. Failure to confirm the presence of a retrovirus in cultured lymphocytes from patients with Kawasaki syndrome. *Pediatric Research*. May 1991;29(5):417-9. doi:10.1203/00006450-199105010-00001
69. Nagata S. Causes of Kawasaki Disease-From Past to Present. *Frontiers in Pediatrics*. 2019;7:18. doi:10.3389/fped.2019.00018
70. Leung DY, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome. *Lancet*. Dec 4 1993;342(8884):1385-8. doi:10.1016/0140-6736(93)92752-f
71. Yoshioka T, Matsutani T, Toyosaki-Maeda T, et al. Relation of streptococcal pyrogenic exotoxin C as a causative superantigen for Kawasaki disease. *Pediatric Research*. Mar 2003;53(3):403-10. doi:10.1203/01.Pdr.0000049668.54870.50
72. Burns JC, Hsieh LE, Kumar J, et al. Characterization of circulating immune cells in acute Kawasaki disease suggests exposure to different antigens. *Clinical and Experimental Immunology*. Dec 2020;202(3):263-272. doi:10.1111/cei.13506
73. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. *Cell*. May 14 2020;181(4):905-913.e7. doi:10.1016/j.cell.2020.04.004

74. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. Mar 13 2020;367(6483):1260-1263. doi:10.1126/science.abb2507
75. Hui KPY, Cheung MC, Perera R, et al. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *The Lancet Respiratory Medicine*. Jul 2020;8(7):687-695. doi:10.1016/s2213-2600(20)30193-4
76. Bronstein DE, Dille AN, Austin JP, Williams CM, Palinkas LA, Burns JC. Relationship of climate, ethnicity and socioeconomic status to Kawasaki disease in San Diego County, 1994 through 1998. *Pediatric Infectious Diseases*. Nov 2000;19(11):1087-91. doi:10.1097/00006454-200011000-00012
77. Bell DM, Brink EW, Nitzkin JL, et al. Kawasaki syndrome: description of two outbreaks in the United States. *New England Journal of Medicine*. Jun 25 1981;304(26):1568-75. doi:10.1056/nejm198106253042603
78. Dean AG, Melish ME, Hicks R, Palumbo NE. An epidemic of Kawasaki syndrome in Hawaii. *Journal of Pediatrics*.. Apr 1982;100(4):552-7. doi:10.1016/s0022-3476(82)80751-8
79. Rowley AH. Is Kawasaki disease an infectious disorder? *International Journal of Rheumatic Diseases*. Jan 2018;21(1):20-25. doi:10.1111/1756-185x.13213
80. Rodó X, Ballester J, Cayan D, et al. Association of Kawasaki disease with tropospheric wind patterns. *Scientific Reports*. 2011;1:152. doi:10.1038/srep00152
81. 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*. Jun 22 2021;143(25):2508-2510. doi:10.1161/circulationaha.121.054785
82. CDC.gov. About Kawasaki disease. CDC.gov. <https://www.cdc.gov/kawasaki/about.html>
83. Green MS. The male predominance in the incidence of infectious diseases in children: a postulated explanation for disparities in the literature. *International Journal of Epidemiology*. Apr 1992;21(2):381-6. doi:10.1093/ije/21.2.381
84. Jiang L, Tang K, Irfan O, Li X, Zhang E, Bhutta Z. Epidemiology, Clinical Features, and Outcomes of Multisystem Inflammatory Syndrome in Children (MIS-C) and Adolescents-a Live Systematic Review and Meta-analysis. *Current Pediatric Reports*. 2022;10(2):19-30. doi:10.1007/s40124-022-00264-1

85. Zahornacky O, Porubčín Š, Rovnakova A, Jarcuska P. Multisystem Inflammatory Syndrome in Adults Associated with Recent Infection with COVID-19. *Diagnostics (Basel)*. Mar 4 2023;13(5)doi:10.3390/diagnostics13050983
86. 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. *Journal of Medical Virology*. Jul 2021;93(7):4358-4369. doi:10.1002/jmv.26951
87. Ae R, Makino N, Kosami K, Kuwabara M, Matsubara Y, Nakamura Y. Epidemiology, Treatments, and Cardiac Complications in Patients with Kawasaki Disease: The Nationwide Survey in Japan, 2017-2018. *Journal of Pediatrics*. Oct 2020;225:23-29.e2. doi:10.1016/j.jpeds.2020.05.034
88. Davis RL, Waller PL, Mueller BA, Dykewicz CA, Schonberger LB. Kawasaki syndrome in Washington State. Race-specific incidence rates and residential proximity to water. *Archives of Pediatric and Adolescent Medicine*. Jan 1995;149(1):66-9. doi:10.1001/archpedi.1995.02170130068016
89. Padilla LA, Collins JL, Idigo AJ, Lau Y, Portman MA, Shrestha S. Kawasaki Disease and Clinical Outcome Disparities Among Black Children. *Journal of Pediatrics*. Feb 2021;229:54-60.e2. doi:10.1016/j.jpeds.2020.09.052
90. 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. *Frontiers in Pediatrics*. 2020;8:626182. doi:10.3389/fped.2020.626182
91. Middelburg JG, Crijnen TEM, D'Antiga L, et al. Association of Ethnicity With Multisystem Inflammatory Syndrome in Children Related to SARS-CoV-2 Infection: An International Case-Referent Study. *Frontiers in Pediatrics* 2021;9:707650. doi:10.3389/fped.2021.707650
92. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *New England Journal of Medicine*. Sep 6 2001;345(10):747-55. doi:10.1056/NEJMra993360
93. Burns JC, Franco A. The immunomodulatory effects of intravenous immunoglobulin therapy in Kawasaki disease. *Expert Review of Clinical Immunology*. 2015;11(7):819-25. doi:10.1586/1744666x.2015.1044980
94. Ephrem A, Misra N, Hassan G, et al. Immunomodulation of autoimmune and inflammatory diseases with intravenous immunoglobulin. *Clinical and Experimental Medicine*. Dec 2005;5(4):135-40. doi:10.1007/s10238-005-0079-y

95. Diao G, Huang J, Zheng X, et al. Prostaglandin E2 serves a dual role in regulating the migration of dendritic cells. *International Journal of Molecular Medicine*. Jan 2021;47(1):207-218. doi:10.3892/ijmm.2020.4801
96. von Gunten S, Schaub A, Vogel M, Stadler BM, Miescher S, Simon HU. Immunologic and functional evidence for anti-Siglec-9 autoantibodies in intravenous immunoglobulin preparations. *Blood*. Dec 15 2006;108(13):4255-9. doi:10.1182/blood-2006-05-021568
97. Hoffmann JHO, Enk AH. High-Dose Intravenous Immunoglobulin in Skin Autoimmune Disease. *Frontiers in Immunology*. 2019;10:1090. doi:10.3389/fimmu.2019.01090
98. Broderick C, Kobayashi S, Suto M, Ito S, Kobayashi T. Intravenous immunoglobulin for the treatment of Kawasaki disease. *Cochrane Database Systematic Review*. Jan 25 2023;1(1):Cd014884. doi:10.1002/14651858.CD014884.pub2
99. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Archives of Disease in Childhood*. Jan 2014;99(1):74-83. doi:10.1136/archdischild-2012-302841
100. Rambabu N, Mathew MJ, Kaveri SV, Bayry J. Boolean analysis of the transcriptomic data to identify novel biomarkers of IVIG response. *Autoimmunity Reviews*. Jul 2021;20(7):102850. doi:10.1016/j.autrev.2021.102850
101. Son MBF, Gauvreau K, Tremoulet AH, et al. Risk Model Development and Validation for Prediction of Coronary Artery Aneurysms in Kawasaki Disease in a North American Population. *Journal of the American Heart Association*. Jun 4 2019;8(11):e011319. doi:10.1161/jaha.118.011319
102. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database Systematic Review*. Jan 27 2017;1(1):Cd011188. doi:10.1002/14651858.CD011188.pub2
103. Vukomanovic V, Krasic S, Prijic S, et al. Recent Experience: Corticosteroids as a First-line Therapy in Children With Multisystem Inflammatory Syndrome and COVID-19-related Myocardial Damage. *The Pediatric Infectious Disease Journal*. Nov 1 2021;40(11):e390-e394. doi:10.1097/inf.00000000000003260
104. Yamaguchi Y, Takasawa K, Irabu H, et al. Infliximab treatment for refractory COVID-19-associated multisystem inflammatory syndrome in a Japanese child. *Journal of Infection and Chemotherapy*. Jun 2022;28(6):814-818. doi:10.1016/j.jiac.2022.01.011

105. Licciardi F, Covizzi C, Dellepiane M, et al. Outcomes of MIS-C patients treated with anakinra: a retrospective multicenter national study. *Frontiers in Pediatrics*. 2023;11:1137051. doi:10.3389/fped.2023.1137051
106. Cannon L, Campbell MJ, Wu EY. Multisystemic Inflammatory Syndrome in Children and Kawasaki Disease: Parallels in Pathogenesis and Treatment. *Current Allergy and Asthma Reports*. Jun 2023;23(6):341-350. doi:10.1007/s11882-023-01083-0
107. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. Aug 7 2020;369(6504):718-724. doi:10.1126/science.abc6027

CURRICULUM VITAE

