Severe COVID-19, multisystem infammatory syndrome in children, and Kawasaki disease:

immunological mechanisms, clinical manifestations and management

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Abstract

I. Multisystem infammatory syndrome (MIS-C) is a pediatric hyperinflammation disorder caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

II. Some of the clinical manifestations of MIS-C mimic Kawasaki disease (KD) shock syndrome.

III. MIS-C develops 4–6 weeks following SARS-CoV-2 infection

IV. Though it has multisystem involvement, it is the cardiovascular manifestations that are most prominent

V. its immunopathogenesis is not fully elucidated

VI. it has some overlap with KD but immunopathogenesis is still unclear

VII. intravenous immunoglobulin and high-dose corticosteroids as frst-line treatment

VIII. Mortality rates of MIS-C are lower compared to adult forms of severe COVID-19 disease.

Background

I. Kawasaki disease (KD) is a medium vessel vasculitis of undetermined etiology usually affecting children below 5 years

II. As far back as 2004 that an unidentified respiratory infectious agent with tropism to vascular tissue, likely a virus, could be linked to the etiology of KD.

III. There has also been a noticeable increase in incidence of 'Kawasaki-like illness' in association with Coronavirus disease 2019 (COVID-19) pandemic

IV. Several terminologies have been used to describe this condition:

- Kawasaki-like syndrome (KLS)
- Atypical Kawasaki disease
- Incomplete Kawasaki disease
- SARS-CoV-2-induced Kawasaki-like Hyper-inflammatory Syndrome (SCiKH Syndrome)
- Kawa-COVID-19

Table 1 Case definitions of hyper-inflammatory syndromes associated with SARS-CoV-2

Parameter	World Health Organization [16]	Centers for Disease Control and Prevention (United States) [15]	Royal College of Paediatrics and Child Health (UK) [17]
Terminology	Multisystem inflammatory disorder in children and adolescents	Multisystem inflammatory syndrome in children (MIS-C)	Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)
Age	0–19 years	0–21 years	Pediatric age group
Clinical case definition	Fever and 2 of the following: (i) Rash or bilateral non-purulent conjunctivitis or mucocutaneous signs (oral, hands or feet) (ii) Hypotension or shock (iii) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated Troponin/NT-pro-BNP) (iv) Evidence of coagulopathy (by PT, PTT, elevated D-dimers) (v) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)	Fever for at least 24 h ≥ 38.0 °C and (i) Severe illness necessitating hospitalization (ii) 2 or more organ systems affected (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and neurological)	Persistent fever and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features, which may include children fulfilling full or partial criteria for Kawasaki disease
Laboratory criteria of inflammation	Elevated ESR, CRP, or procalcitonin	Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, neutrophilia, lymphopenia, and low albumin	Neutrophilia, elevated CRP and lymphopenia
Evidence of SARS-CoV-2 infection	Evidence of COVID-19 infection (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to onset of symptoms	SARS-CoV-2 PCR testing may be positive or negative

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* Interlukin: *LDH* lactate dehydrogenase, *RT-PCR* reverse transcription-polymerase chain reaction

Definitions have been proposed by World Health Organization [16], Centers for Disease Control and Prevention [15] and Royal College of Paediatrics and Child Health [17]

MIS-C and KD, however, differ in several clinical features:

- Gastrointestinal complications, shock and coagulopathy are more common in patients with MIS-C, but are unusual in classic KD
- Classic KD is common in North East Asian countries, whereas MIS-C has been reported more commonly in patients of African, Hispanic or Latino ethnicity
- KD is common in children below 5 years, whereas MIS-C is more common in older children
- however, it is unclear whether the immunological mechanisms behind hyperinflammation of MIS-C are the same as that in adults with COVID-19
- Cytokine storm induced hyperinflammation in adult COVID-19 is usually seen within 2 weeks, whereas MIS-C has been more commonly reported after 2 weeks of SARS-CoV-2 infection.

COVID-19

- Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus SARS-CoV-2, which is a member of Betacoronavirus family
- largely asymptomatic in most individuals
- A minority of patients develop severe disease : elderly patients and in patients with comorbidities such as diabetes and cardiovascular disease
- Transmissibility of SARS-CoV-2 is higher when compared to other coronaviruses such as SARS-CoV (2002) and Middle East Respiratory Syndrome (MERS)

Phenotypes of COVID-19 infection observed in children and diferences from adult disease

- SARS-CoV-2 enters the host cell through binding of its spike (S) protein to the ACE2 receptor. This entry is facilitated by priming of S-protein through proteases (e.g., TMPRSS2).
- Recent studies have shown that adults have higher expression of ACE2 and TMPRSS2 on alveolar lining cells as compared to children.
- Pediatric COVID-19 typically presents with mild symptoms such as cough, fever, sore throat and diarrhea. Lower respiratory tract symptoms are usually less prominent in children as compared to adults.
- In childern progression to acute respiratory distress syndrome (ARDS), which is a hallmark of adult COVID-19 disease, is even less common.
- Mortality rate in children as compared to adults 0.1% versus 5-15%.

Table 2 Comparison of immune alterations between pediatric and adult COVID-19

Parameter	Pediatric COVID-19	Adult COVID-19
ACE2 expression	Low levels	High levels
Type I interferon	Rapidly elevated upon infection	Delayed response
Lymphocytes	Normal or high counts	Decreased
Cytotoxic T cells	Normal or high levels	Decreased
Anti-SARS-CoV-2 antibodies	High titres	Relatively low titres
Neutrophil infiltration	Low	High
Cytokine storm	Not common	Seen in patients with moderate and severe illness
Anti-inflammatory cytokine and regulatory T cells	High	Low
Severe disease	1%	10–20%

ACE2 angiotensin-converting enzyme, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2

Clinical correlation of immune response in pediatric COVID-19

- Children with mild COVID infection have been reported to have increased number of IgG producing B cells as well as lower levels of acute phase reactants such as C-reactive protein (CRP) and IL-6.
- Lymphocytopenia, on the other hand, is more common in adult patients with severe COVID-19 infection as compared to children
- Children with pneumonia in the setting of COVID-19 have low levels of serum IgA and regulatory (CD4+CD25+) T cells, increased levels of high sensitivity (hs)-CRP, IL-10 and procalcitonin
- SARS-CoV-2 infection also causes chilblains, also known as ‘COVID toes It probably results from vascular damage and necrosis of SARS-CoV-2-infected endothelial cells resulting in ischemia.
- In summary, children with COVID-19 tend to have an appropriate early innate and humoral immune response to HCoV infections to clear the virus, followed by a less intense late immune response in majority

Treatment of pediatric COVID-19

- Treatment of COVID-19 is largely supportive
- Supportive therapy includes maintenance of adequate hydration, appropriate calorie intake and psychosocial support. For fever, paracetamol is recommended.
- patients having severe symptoms require hospitalization and intensive care
- these patients are usually put on broad-spectrum antimicrobials and antivirals (e.g., remdesivir and lopinavir/ritonavir)
- Few patients with severe COVID-19 disease and ARDS may require immunomodulatory therapies for the putative hyper-infammatory state. These therapies include corticosteroids and biologics such as tocilizumab and anakinra.

clinical features of multisystem infammatory syndrome in children (MIS-C)

- the features that are common to all include the presence of fever, hyper-inflammatory state and organ dysfunction
- Fever , cutaneous manifestations, abdominal symptoms and cardiovascular collapse.
- typically, this entity is seen in older children (>5 years) and median age of patients in various studies has ranged from 7.5 to 10 years
- Gastrointestinal manifestations are very common and include abdominal pain, diarrhea and vomiting
- Neurological features (e.g., headache, meningeal signs and altered sensorium)

A large experience from the United Kingdom (UK) [42]. They reported 58 patients with PIMS-TS and identified three different types of clinical presentations

- **Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2**
- I. Persistent fever and elevated inflammatory markers:
- • These patients did not have features of organ dysfunction, KD or toxic shock syndrome (TSS)
- II. Fever along with cardiovascular collapse and elevated cardiac biomarkers:
- • These patients had predominant cardiac manifestations including left ventricular dysfunction and arrhythmias
- • Cardiac troponin and pro-BNP were significantly elevated in these patients
- III. Patients presenting as KD or KD shock syndrome (KDSS):
- • These patients fulfilled the American Heart Association diagnostic criteria for KD

cardiovascular complications

- The most prominent manifestations in patients with MIS-C
- Cardiac biomarkers including NT-pro-BNP and troponin levels are extremely high compared to historical KD cohorts and indicate heart failure and myocardial damage in MIS-C
- Symptomatic myocarditis in 40–80% of patients with MIS-C and is seen in less than 5% of patients with KD
- Coronary artery abnormalities (CAAs) have been reported in 9–24% of patients with MIS-C
- CAAs are in form of dilatation or small-sized aneurysms in most patients.
- Pericarditis, pericardial efusion and valvular regurgitation have also been reported
- Electrocardiographic abnormalities include prolonged PR interval, T wave and ST segment changes.

Diferential diagnosis

- Diagnosis of MIS-C should be considered in children presenting with unexplained high-grade fever lasting more than 4 days
- These have been highlighted in Table3

Table 3 Comparison between multisystem inflammatory syndrome in children (MIS-C), Kawasaki disease (KD), toxic shock syndrome (TSS) and severe COVID-19 disease in children and adults

Characteristics	MIS-C	KD	TSS	Severe COVID-19 in children without MIS-C	Severe COVID-19 in adults
Age of presentation	Usually in children aged 8–10 years	Usually in children below 5 years (slightly older in KDSS)	Usually in children above 10 years	Usually in adolescents	Fatality rates higher in advanced age
Gender difference	Male > female	Male > female	Male < female	Male = female	Male > female
Affected ethnicity	Hispanic/Latino/African American > White	East Asian	No ethnic variation known	No difference	No difference
Fever	Present	Present	Present	Present	Present
Cutaneous signs	Similar to KD but full range of spectrum seen in < 50%	Typical signs seen in majority of patients	Usually erythroderma and petechiae	Usually absent; rarely, chilblain like lesions on toes (COVID toes) have been reported in adolescents	Acro-ischemia in fingers and toes, cyanosis, cutaneous bullae, dry gangrene and maculopapular rash
Lymphadenopathy	Not common	More common	Less common	Not known	Less common
Hemodynamic instability and ICU support	Hemodynamic instability present in almost all patients	Less than 5% of patients have KDSS	Usually present	Seen in patients with multiorgan dysfunction	5–12% of all cases
Cardiovascular Complications	Cardiac dysfunction is seen at presentation; severe myocarditis and pericarditis are more common; CAAs are usually restricted to mild dilatation and small-sized aneurysms	Symptomatic myocarditis is not common; both coronary artery dilatation and aneurysms are seen	Myocardial dysfunction, CAAs and valvular regurgitation are usually not seen	Myocardial dysfunction, CAAs and valvular regurgitation are usually not seen	Myocardial dysfunction, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events are reported
Predominant manifestations	Gastrointestinal manifestations (abdominal pain, diarrhea) are prominent and present in > 80% patients; some present with acute surgical abdomen	Gastrointestinal symptoms are usually not prominent	Rash, hypotension	Cough, respiratory distress may be present; gastrointestinal symptoms are less common	Cough, respiratory distress is common
Inflammatory markers	Markedly increased levels of inflammatory markers compared to classical KD; lymphopenia common; cytokine storm is more severe; extremely high levels of NT-pro-BNP, Troponins and D-dimers	Neutrophilic leukocytosis is usual	Neutrophilic leukocytosis is usual	Lymphopenia and neutropenia may be seen in 1/3rd patients; however, increased lymphocyte counts may also be seen	Inflammatory markers are raised; lymphopenia is common
Organ dysfunction	Multiorgan dysfunction seen	Multiorgan dysfunction is not common	Renal and CNS involvement is common	ARDS; MAS, shock are common	ARDS, heart failure, renal failure, liver damage, shock, and multiorgan failure are common

Table 3 (continued)

Characteristics	MIS-C	KD	TSS	Severe COVID-19 in children without MIS-C	Severe COVID-19 in adults
Underlying etiology	Putative post-infectious syndrome; SARS-CoV-2 serology is usually positive; in seronegative patients there is usually history of contact with an individual having COVID-19 infection	No identifiable cause	Focus of staphylococcal or streptococcal infection often present	Underlying comorbidity may be present; SARS-CoV-2 RT-PCR usually positive	Underlying comorbidity usually leads to severe disease; SARS-CoV-2 RT-PCR usually positive
Anti-HCoV antibodies	70–90%	Paucity of data	No data	Nearly 90% of infected children develop antibodies	Seen in almost all patients after 2 weeks of infection [101][a]
Autoantibodies	Few reports	Less common	No data	No data	Noted in only one study[b] [102]
T cells	Lymphopenia	Involvement of cytotoxic T cells	Lymphopenia	Usually unaltered	Lymphopenia in severe disease
Co-morbidities as risk factors	Possibly underlying immunodeficiency states	Not common; rarely seen with primary immunodeficiency and occasionally seen in context of acquired immunodeficiency	Usually not significant	Co-morbidities (e.g., malignancy, chronic lung diseases, and neurological disorders) are associated with severe forms of disease	Co-morbidities (e.g., hypertension, diabetes mellitus, chronic heart or lung disease) are associated with severe forms of disease
Management	IVIg; steroids; IL-1 blockers; IL-6 inhibitors	IVIg; steroid; IL-1 blockers	Antibiotics, IVIg	Antiviral agents, antibiotics, IVIg, steroids, IL-6 inhibitors	HCQS, IL-6 inhibitors; steroids; convalescent plasma; antiviral therapies

ARDS acute respiratory distress syndrome, *CAA* coronary artery aneurysm, *CNS* central nervous system; *ICU* intensive care units; *KDSS* Kawasaki disease shock syndrome, *MAS* macrophage activation syndrome, *TSS* toxic shock syndrome, *IVIg* intravenous immunoglobulin, *HCQ* hydroxychloroquine

References: [19, 68], [a]Long et al. Nat Med. 2020 Jun;26(6):845–848, [b]Gazzaruso C et al. Clin Rheumatol. 2020;39(7):2095-2097

Laboratory features

- complete blood counts, liver function tests, renal functions tests, and an assay of inflammatory markers
- MAS should be considered whenever there is rapid clinical deterioration
- Majority of patients with MIS-C appear to have a hyper-inflammatory state that manifests as neutrophilic leukocytosis, raised erythrocyte sedimentation rates, hyponatremia, hypertriglyceridemia, elevated levels of CRP, procalcitonin, d-dimer and serum ferritin
- Patients with MIS-C usually have lower platelet counts and higher ferritin levels as compared to patients with KD.
- lymphopenia has been noted in patients with MIS-C, neutrophilic leukocytosis is the norm in KD
- one-third of patients who were negative on both tests (RT-PCR or serology)
- That patients with MIS-C had higher levels of IgG SARSCoV-2 receptor-binding domain.
- Both NT-pro-BNP and cardiac troponin levels are extremely high in patients with MIS-C compared to KD
- 2D-echocardiography should be carried out for identification of myocarditis, pericarditis, valvular abnormalities and CAAs

Treatment

- Treatment regimens have been extrapolated from guidelines for management of patients with KD
- intravenous immunoglobulin (IVIg) and/or high-dose corticosteroids as first-line therapy in these patients
- .Approximately 30–80% patients do not respond to IVIg alone
- Classic KD where IVIg resistance has been seen in less than 15% patients
- Intravenous pulse methylprednisolone (10–30 mg/kg/day for 3–7 days followed by gradual tapering of oral prednisolone) has been found to be useful
- second dose of IVIg, anakinra, tocilizumab and infliximab

Complications and outcome

- MIS-C have been reported to have propensity for multisystem involvement ,myocarditis, MAS and renal impairment
- MIS-C is a hyper-inflammatory state and can progress to MAS/cytokine storm syndrome
- Higher age, and a serum ferritin>1400 μg/L were the best discriminators for severe disease
- Myocarditis can evolve rapidly and needs to be identified early(i.e., IVIg and high-dose corticosteroids). Follow-up echocardiography at 6 weeks was normal
- CAAs of MIS-C are usually in the form of ectasia or small dilatations
- Mortality rate of MIS-C was 2% and lower compared to adults

Kawasaki disease (KD), MIS-C and COV-HI in adults and pediatric COVID-19

- **KD and HCoV**
- Approximately 9% of patients with KD have recent history of respiratory infections (usually rhinovirus, adenovirus and influenza).
- Interval between onset of respiratory syndrome and development of KD is approximately 2 weeks
- These patients often has incomplete KD and is associated with high frequency of coronary aneurysms
- patients with KD and influenza co-infection longer duration of fever and delays in diagnosis

Immunological alterations in MIS-C, a severe pediatric COVID-19 disease

- SARS-CoV-2 associated MIS-C usually appears a few weeks after onset of infection(36–45 days).
- Higher number of mucosal homing T cells and higher expression of IL-17 were also seen in pediatric COVID19 with MIS-C
- Cytokine profile showed that levels of IL-10 and TNF-α were higher in MIS-C compared to severe COVID-19 without MIS-C
- MIS-C may be a post-infectious, immunologically mediated sequel of COVID-19

Similarities between MIS-C and KD

- Both have significant cytokine storm that results in systemic inflammation(myocarditis)
- Both have small and medium vessel vasculitis (diarrhea and abdominal pain)
- Both have autoantibodies (Target antigens in mucosal and cardiac tissues)
- Autoantibodies or antibodies to SARS-CoV-2 may be contributing to disease pathogenesis in MIS-C and KD

Differences between MIS-C and COV-HI in adults

- Hyperinflammation-induced cytokine storm in covid-HI patients predominantly involves the lungs resulting in ARDS, whereas MIS-C is a multiorgan cytokine storm that usually spares the lungs
- COV-HI when patients with COVID-19 have CRP values>150 mg/L or when serum ferritin level is>1500 µg/L
- Objective criteria for COV-HI based on fever, hematological dysfunction, macrophage activation, liver involvement, coagulation abnormalities and hypercytokinemia
- MSI-A is predominant involvement of cardiovascular and gastrointestinal systems
- LB test in MSI-A include elevated inflammatory parameters (e.g., CRP and ferritin), raised d-dimer levels and lymphocytopenia

Serological findings in MIS-C, KD and severe COVID-19

- Approximately 70% of children with MIS-C have a positive antibody response against SARS-CoV-2. The RT-PCR test is positive in up to 60%
- The reasons for low positivity rate of RT-PCR in patients with MIS-C :
- 1. Interval between SARS-CoV-2 exposure and development of MIS-C varies from 2 to 4 weeks (post-infectious inflammatory syndrome).
- 2. Positivity rate of serology is reportedly higher than that of RT-PCR amongst those tested (%10.7 versos %1.8)

Conclusion

- MIS-C is a hyper-inflammatory syndrome affecting multiple organs and is triggered by SARS-CoV-2 infection.
- It is usually seen 2–4 weeks following infection.
- Adaptive immune mechanisms have a major role to play in pathogenesis of this condition.
- Although clinical manifestations of MIS-C and KD may be overlapping, these appear to be two distinct clinical entities.


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