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Review Article

Multisystem inflammatory syndrome in children: A dysregulated autoimmune disorder following COVID-19

Ping-Ing Lee [a,*], **Po-Ren Hsueh** [b,c,d,e]

[a] *Department of Pediatrics, National Taiwan University Children's Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[b] *Division of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[c] *Department of Laboratory Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[d] *Ph.D Program for Aging, School of Medicine, China Medical University, Taichung, Taiwan*
[e] *Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

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Abstract Multisystem inflammatory syndrome in children (MIS-C) is a dysregulated autoimmune-mediated illness in genetically susceptible patients following COVID-19 with an interval of 2–6 weeks. The median age of patients with MIS-C is 6–11 years. Most common manifestations are involvement of gastrointestinal tract, cardiovascular system, hematological system, and mucocutaneous system. Respiratory tract, neurological system, musculoskeletal system, and kidney are less frequently affected. Mucocutaneous manifestations and coronary artery abnormalities characteristic for Kawasaki disease (KD) may be observed in a significant proportion of MIS-C patients that may make the differential diagnosis be difficult for some patients, especially in the post-pandemic era. The mortality rate is 1–3%. Management and prognosis of MIS-C are similar to that of KD. MIS-C and KD may share a common pathogenic process. Based on the observation of MIS-C-like illness in uninfected neonates, i.e. multisystem inflammatory syndrome in neonates, both MIS-C and KD may be a consequence of dysregulated, over-exaggerated humoral immune responses triggered by a specific infectious agent.

* Corresponding author. Department of Pediatrics, National Taiwan University Children's Hospital, No.8, Chung Shan S. Rd., Taipei 10041, Taiwan.
E-mail address: pinging@ntu.edu.tw (P.-I. Lee).

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Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, emerged at the end of 2019, has been associated with widespread mortality and morbidity.[1—4] Seroprevalence study in the United States showed that seropositive rates of SARS-CoV-2 antibody are higher in children than in adult.[5] However, infected children have a lower incidence of both symptomatic and severe infections when compared with the adult population.[6] Beginning in April 2020, cases of children with a severe inflammatory syndrome following COVID-19 with features similar to Kawasaki disease (KD) were reported from Italy, the United Kingdom and New York. This newly discovered illness was named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 in the United Kingdom, and multisystem inflammatory syndrome in children (MIS-C) by the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).[7,8]

MIS-C develops several weeks after the infection rather than during the acute stage of COVID-19. Mucocutaneous manifestations of KD may be observed in MIS-C with a lower frequency. On the other hand, a predominant gastrointestinal involvement and a more frequent involvement of myocardium are unique for MIS-C. Therefore, the clinical features are both similar and distinct from KD.[9] This post-COVID-19 complication are associated with some morbidity and mortalities. Exploring the pathogenesis of MIS-C may shed light to the pathogenesis of COVID-19 and may also help to find out the mysterious origin of KD.

Case definition

There is not a universally accepted case definition for MIS-C. The most commonly adopted case definitions are those proposed by CDC and by WHO (Table 1).[9,10] Case definitions of MIS-C by the two organizations include fever in children with elevated markers of inflammation, multisystem involvement, evidence of recent SARS-CoV-2 infection and exclusion of other diagnoses. Major differences between the 2 definitions include age ($\leq$19 years for WHO vs. $\leq$ 20 years for CDC), duration of fever ($\geq$3 days for WHO vs. $\geq$ 1 day for CDC), requiring hospitalization for CDC and more extensive and specific laboratory criteria for the CDC definition.[8]

CDC criteria describe abnormal laboratory finding in more details, while WHO criteria put more emphasis on characteristic findings of MIS-C, including mucocutaneous manifestations, gastrointestinal symptoms, coagulopathy, and heart problems (Table 1). A requirement of fever $\geq$3 days in WHO criteria may miss some patients with MIS-C because a small percentage of characteristic cases may have a fever lasting for no more than 3 days.[11,12]

A contact history with COVID-19 patients within 4 weeks prior to the onset of symptoms in WHO criteria may also underestimate the exact incidence because reported intervals between COVID-19 and MIS-C are usually 2—6 weeks with a median of 4 weeks.[8,9] On the other hand, a requirement of hospitalization in CDC criteria may miss some cases with mild MIS-C. A significant proportion of the reported MIS-C cases could not fulfil the diagnostic criteria for MIS-C.[13]

Epidemiological features

Estimated incidences of MIS-C in young individuals infected with SARS-CoV-2 were 0.4—5.5/100,000.[8,14,15] The incidence is higher in some ethnic groups, including Black, Hispanic, Latino, and Pacific Islander persons.[8,15—19] Reported incidences in Asian children are similar or slightly higher that in white children. This is in contrast to an

Table 1 Case definitions of multisystem inflammatory syndrome in children.

Proposed organization	U.S. CDC	WHO
Age	$\leq$20 years	$\leq$19 years
Fever	$\geq$38°C or subjective fever for $\geq$24 h	$\geq$3 days
Laboratory evidence of inflammation	Such as elevated ESR, CRP, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, neutrophil; reduced lymphocytes, low albumin	Such as elevated ESR, CRP, procalcitonin
Multisystem involvement	$\geq$2 systems: cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological	$\geq$2 manifestations: 1. rash, conjunctivitis, mucocutaneous signs; 2. hypotension/shock; 3. myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities; 4. coagulopathy (by PT, PTT, d-dimers); 5. acute gastrointestinal problems (diarrhea, vomiting, abdominal pain)
Requiring hospitalization	Yes	No
Evidence of COVID-19	RT-PCR, antigen test, serology test, or contact with patients with COVID-19	RT-PCR, antigen test, serology test, or contact with suspected or confirmed patients with COVID-19 within 4 weeks prior to the onset of symptoms
Other plausible diagnosis	No other microbial cause of inflammation	No alternative plausible diagnosis

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactic acid dehydrogenase; IL-6, interleukin-6; PT, prothrombin time; PTT, partial thromboplastin time.

especially high incidence of KD in Asian children.[7] The incidence of MIS-C is higher in children living in socioeconomically deprived condition.[16,18,19] Comorbid conditions are present in 27%—36% of patients.[7,12,13]

MIS-C occurs predominantly in male with a male to female ratio of about 3:2.[7,13,14] The median age of patients with MIS-C is 6—11 years[7,8,13,20,21] Similar illness, named as MIS in neonates (MIS-N), may occur within one week of life in neonates born to mothers having COVID-19 during pregnancy.[22,23] Rare cases with similar symptoms have also been reported in adults, referring to as MIS in adults (MIS-A).[8,24] MIS-N and MIS-A have some different clinical characteristics from those observed in patients with MIS-C.

Reports from Israel, the U.S. and South Africa suggest that Delta and/or Omicron variants may be associated with a lower incidence and a milder illness of MIS-C.[14,25,26] It is not known whether the observed difference is a consequence of some unique biological properties of variants, or simply a result of a gradually expanding population with immunity against SARS-CoV2. Despite emerging variants may escape from human immunity and cause breakthrough infection, MIS-C in later epidemic waves tends to have a lower incidence of severe complications.[25]

Clinical manifestations

MIS-C occurs at a median of 4 weeks (range 2—6 weeks) following COVID-19.[8,9] Most preceding COVID-19 illnesses are mild or asymptomatic.[14] Most common manifestations are involvement of gastrointestinal tract, cardiovascular system, hematological system, and mucocutaneous system. Respiratory tract, neurological system, musculoskeletal system, and kidney are less frequently affected.[12] Cardiac and neurologic anomalies are more frequently observed in older patients than in children younger than 5 years. Neuromuscular symptoms are not common in MIS-C.[7,8,11—14,20,27,28]

According to the case definition, fever is present in 100% of patients and usually lasts for 1—7 days.[7,11—14,20,27] However, one meta-analysis shows that fever is absent in 9% of reported MIS-C patients.[29] The gastrointestinal system is the most commonly involved organ system. Vomiting, diarrhea and abdominal pain are reported in over 50% of patients (Table 2).[7,8,11—14,20,27,29] Rare events of appendicitis, pancreatitis, and intussusception have been reported.[27] Abdominal imaging may show ascites, enlarged mesenteric lymph nodes, appendiceal inflammation and wall thickening of intestinal tract.[30]

More than half of MIS-C patients are associated with hypotension and shock that frequently require intensive care. Hypotension may result from myocardial dysfunction or preload reduction due to inflammation-associated vasodilation.[7,8,11—14,20,27,29]

Mucocutaneous symptoms/signs, similar to those observed in KD, occur more frequently in children 0—5 years of age than older patients.[13,14,27,31] Almost all mucocutaneous symptoms/signs of KD have been described in patients with MIS-C, including conjunctival injection, red and fissured lips, strawberry tongue, cervical lymphadenopathy, skin rashes, palmar/plantar edema and erythema, and desquamations of digits.[29,32] A variety of skin rashes has been described, including erythematous maculopapules, annular plaques, morbilliform eruptions, erythroderma, and urticarial-like lesions.[10] Infrequently, the skin lesion may be petechial or purpuric.[32] The skin rashes may locate at all parts of the body, and may be associated with desquamations. Two characteristic cutaneous manifestations of KD, erythematous change of *Bacillus Calmette-Guérin* scar and perineal erythema and desquamation, have also been reported in rare cases with MIS-C.[33—36]

Elevated inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin, can be detected in most patients with MIS-C. High ferritin and high fibrinogen levels are also frequent findings (Table 2).[7,20,29] Myocardial injury and hypotension are predominant features of MIS-C, over half of patients has elevated troponin and/or pro-brain natriuretic peptide (proBNP) level.[37,38] Some patients may present with left ventricle dysfunction, arrhythmia and other abnormal electrocardiographic findings. Cardiac magnetic resonance shows that MIS-C-associated myocarditis is characterized by global myocardial inflammation and edema, whereas only regional inflammation and edema were noted in COVID-19 myocarditis.[39] The incidence of coronary artery dilatation varied between 10% and 48% in different reports (Table 2).[20,37,38] Coronary artery abnormalities were more common in males and in patients with mucocutaneous lesions.[17]

Anemia, lymphopenia, increased D-dimer, hypoalbuminemia, abnormal liver function profiles, acute kidney injury, sterile pyuria are also common findings.[7,20,40,41] The extent of laboratory abnormalities was reported to correlate with severity of MIS-C.[12] Because MIS-C is a post-infection complication of COVID-19, only 21%—52% of patients had a positive test for SARS-CoV-2 reverse transcription-polymerase chain reaction at the time of diagnosis (Table 1).[7,20,40,41]

A significant proportion (31%—85%) of patients require intensive care, and some of them need mechanical ventilation and extracorporeal membrane oxygenation. The illness tends to be milder in children younger than five years.[13,14,17,27] Risk factors for intensive care unit admission include the presence of dyspnea, abdominal pain, and elevated levels of CRP, troponin, ferritin, D-dimer, proBNP, interleukin-6, or decreased levels of platelet and lymphocyte.[17]

Clinical characteristics of MIS-C were reported to be slightly different among patients with or without preceding COVID-19-like illness. Patients with preceding illness tended to be older than those without preceding ill. More patients without preceding COVID-19-like illness had hypotension, shock, cardiac dysfunction and need for intensive care. Cough, shortness of breath, and chest pain were more frequently reported in patients with preceding COVID-19.[14]

MIS-N

Neonatal COVID-19 occurs infrequently. The reported perinatal vertical transmission of SARS-CoV-2 varies from 1 to 10% in different studies.[42] Illness similar to MIS-C may also be observed in neonatal period. MIS-N is used to

Table 2 Clinical manifestations of multisystem inflammatory syndrome in children.

Characteristic	Incidence (%)	Reference number
Symptom/sign		
Preceding COVID-19-like illness	25	9
Fever	100	7,11–13, 21, 28, 29, 47, 50
Gastrointestinal symptom	60–100	7, 9, 12, 20, 21, 28, 29, 50, 80
Nausea/vomiting	44–68	7, 8, 13, 17, 20, 21, 29, 47
Diarrhea	40–78	7, 9, 11, 13, 17, 20, 21, 29, 47
Abdominal pain	49–78	7, 9, 11, 13, 17, 20, 21, 29, 47
Cardiac symptom/sign	31–66	7, 9, 12, 28, 50, 80
Hypotension	27–59	7, 11, 13, 47, 80
Shock	40–80	7, 9, 13, 17, 20, 21, 25, 28, 29, 47
Mucocutaneous symptom/sign		
Conjunctival injection	31–83	6, 11–13, 17, 20, 21, 28, 29, 47, 50
Red, fissured lips	37–49	20
Strawberry tongue	11–23	20, 50
Cervical lymphadenopathy	30–70	12, 13, 20, 21, 28, 29, 47, 50
Skin rashes	50–70	7, 11–13, 17, 20, 21, 28, 29, 47, 50
Palmar and plantar swelling/redness, scaling	21–68	12, 13, 20, 21, 28, 29, 50
Respiratory symptom/sign		
Sore throat	7–20	7, 13, 21
Cough	10–41	7, 13, 17, 21, 47, 50
Dyspnea	19–29	7, 13, 27, 28, 47
Chest pain/tightness	11–15	13
Pneumonia by image	13–19	20, 25, 50
Pleural effusion	10–20	12, 20, 25
Neuromuscular symptoms	13–46	7, 9, 13, 20, 29
Headache	24–70	7, 13, 21, 47
Myalgia	17–66	12, 20, 25
Laboratory test		
Anemia	8–49	29
Lymphopenia	37–81	13, 25, 28
Thrombocytopenia	11–31	13, 25
Increased ESR	56–77	13, 29
Increased CRP	93–100	13, 29
Increased procalcitonin	42–100	13
Increased ferritin	54–75	13, 29
Increased troponin	33–95	12-14, 20, 21, 25, 29
Increased proBNP	54–95	12-14, 21, 25, 29
Decreased LVEF by echocardiogram	24–58	12, 14, 20, 21, 47
Myocarditis	29–87	9, 11, 13, 17, 20, 21, 25, 29
Pericardial effusion	13–28	12, 20, 21, 25
Coronary artery dilatation	10–48	9, 12, 13, 17, 20, 21, 25, 28, 47, 50
Increased D-dimer	69–98	9, 13, 29
Increased fibrinogen	26–86	13, 29
Hypoalbuminemia	16–76	13, 29
Increased AST/ALT	43–60	12
Acute kidney injury	10–16	9, 13, 21, 25, 29
Sterile pyuria	50–75	7
RT-PCR (+)	21–52	7, 9, 12, 13, 47
Management		
Intensive care	31–85	7, 9, 11–14, 17, 21, 25, 29, 50, 80
Mechanical ventilator	10–32	7, 9, 11–14, 21, 25, 28, 29, 47, 80
ECMO	2–36	7, 9, 11–14, 21, 24, 29, 80
Death	1–3	7, 9, 12, 13, 17, 21, 25, 28, 29, 47, 50

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; proBNP, pro-brain natriuretic peptide; EKG, electrocardiogram; LVEF, left ventricular ejection fraction; AST, aspartate aminotransferase; ALT, Alanine aminotransferase; RT-PCR, reverse transcription-polymerase chain reaction; ECMO, extracorporeal membrane oxygenation.

describe this condition.[22,23,42,43] Presentations included gastrointestinal symptoms, cardiovascular compromise, respiratory involvement, and fever. In contrast to MIS-C that is associated with 100% occurrence of fever according to diagnostic criteria, fever is present in only 18%—36% of neonates with MIS-N.[22,43] Management is similar to those for MIS-C. Comparing with MIS-C, MIS-N is associated with a worse outcome. The mortality rate is 11% in one review.[43]

About half of MIS-N has a disease onset within 72 h after delivery.[42,43] The illness may result from transplacental maternal COVID-19-induced antibodies, because the virus cannot be detected in affected neonates.[42,44] Late-onset MIS-N, occurring >72 h after delivery, may be caused either by transplacental maternal antibody or by fetal/neonatal infection-associated inflammatory response.[42,43]

MIS-A

MIS-A is used to describe adults with presentations similar to MIS-C. According to CDC, MIS-A is defined as a patient aged ≥21 years hospitalized for ≥24 h, or with an illness resulting in death, who meets the clinical and laboratory criteria.[45] The patient should not have a more likely alternative diagnosis for the illness. Clinical criteria include fever ≥24 h and at least 3 of the following conditions (at least one must be a primary clinical criterion): 1. primary clinical criteria: myocarditis, pericarditis, coronary artery dilatation/aneurysm, new-onset right or left ventricular dysfunction, 2nd/3rd degree atrioventicular block, ventricular tachycardia, rash and non-purulent conjunctivitis; 2. secondary clinical criteria: new-onset neurologic signs and symptoms, shock, hypotension, abdominal pain, vomiting, diarrhea, thrombocytopenia. Laboratory criteria include laboratory evidence of inflammation (elevated levels of at least 2 of the following: CRP, ferritin, interleukin-6, ESR, procalcitonin) and SARS-CoV-2 infection.

The median age of MIS-A is 20—30 years with male predominance. Clinical manifestations are similar to MIS-C. Cardiac dysfunction, gastrointestinal disturbance, mucocutaneous involvement, elevated markers of coagulopathy are common findings.[24,46] Some of them presented with typical features of KD.[24] The mortality rate was reported to be 5%.[46]

Differential diagnosis

The differential diagnosis of MIS-C includes KD, adenovirus infection, sepsis, toxic shock syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, autoimmune disorders, drug reaction with eosinophilia and systemic clinical manifestations.[31,38] Among them, KD is the most important differential diagnosis for MIS-C. Many of their clinical features overlap with each other, and 15%—50% of patients with MIS-C meet the full diagnostic criteria for KD.[8,20,21,29,47]

KD is a systemic vasculitis syndrome in children with obscure etiology. It was first described in 1967 by Dr. Tomisaku Kawasaki, a Japanese pediatrician.[37] Coronary artery abnormality is the most dreaded complication that may lead to mortality or long-term sequelae.[37,48,49] The systemic inflammatory is thought to be triggered by an unidentified infectious agent in some genetically predisposed individuals.[9] Major features of KD include persistent fever for more than 5 days, bilateral conjunctival injection, oral mucosa changes (red and fissured lips, strawberry tongue, pharyngeal injection), cervical lymphadenopathy, skin rashes, indurated edema and redness of palms and soles, desquamations of fingers and toes.[38,48—50]

KD typically occurs in children <5 years old, whereas MIS-C tends to occur at an older age with a median age of 6—11 years.[20] The presence for fever for more than 5 days is a prerequisite for the diagnosis of KD. Patients with MIS-C have a shorter duration of fever, and the diagnosis requires a fever of ≥1 day by CDC criteria.

In general, MIS-C present with a wider spectrum of symptoms.[9] Cardiac, gastrointestinal, and neurological symptoms are more commonly observed in MIS-C than in KD. Abnormal laboratory findings, including elevated cardiac enzymes, coagulopathy, abnormal renal function, lymphopenia and thrombocytopenia, are also more frequently encounter in MIS-C (Table 3).[8,20,28,50,51] Patients with MIS-C tend to have higher level of inflammatory markers than patients with KD, including CRP, fibrinogen, and ferritin.[50]

Myocarditis and shock are more frequent with MIS-C.[31] Shock is present in of 40—80% of patients present with MIS-C,[14,20] while less than 10% of KD present as KD shock syndrome.[20,48,49] The occurrence of coronary artery abnormalities in MIS-C is not limited to patients fulfilling the KD criteria.[8]

All mucocutaneous manifestations characteristics for KD can be observed in MIS-C patients with a lower frequency (Table 3).[8,20,28,29,51] The incidence of skin rashes is slightly lower for MIS-C than for KD. The skin rashes may be macules, papules, erythroderma, or urticarial-like lesions in both disorders.[52] There is no preferential anatomic site of involvement. Petechial or purpuric skin lesions have been described rarely in patients with MIC-S,[32] but no in patients with KD.

At the beginning of COVID-19 pandemic, SARSCoV-2 testing and exposure history are useful to distinguish between MIS-C and KD. However, virological tests may not be useful when most people have either been infected or been vaccinated in the future.[50] A recent COVID-19 illness will be the only reliable evidence for the diagnosis of MIS-C. However, MIS-C frequently follows either asymptomatic or subclinical infections.[14] During the post-pandemic era, it will become more and more difficult to differentiate between MIS-C and KD.

Pathogenesis

The pathogenesis of COVID-19 is still in investigation. COVID-19 is known to be associated with autoimmune phenomenon, including a higher antibody level and other exaggerated immune response in patients with severe COVID-19.[53—56] Similar to KD, MIS-C is considered to be a dysregulated immune response toward SARS-CoV-2 with subsequent cytokine storm in genetically susceptible individuals.[9,20] Generalized endothelial damages result in characteristic features of vasculitis syndrome.[9]

Gene analyses have identified several gene polymorphisms that predispose to the development of MIS-C. All these mutations are linked to exaggerated inflammatory responses.[57—60] A study shows that KD and MIS-C are on the

Table 3 Comparisons of multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease.

Demographics	MIS-C	Kawasaki disease
Age	≤20 years, peak 6–11 years	<5 years
Male: female ratio	3:2	1.5:1
Ethnicity	High incidence in Japan, China, Taiwan, South Korea	High incidence in children of African and Hispanic heritage
Clinical features		
Fever	100% (+), ≥1 day	100% (+), ≥5 days
Conjunctival injection	31%–83%	>90%
Red, fissured lips	30%–50%	>90%
Strawberry tongue	10%	>90%
Cervical lymphadenopathy	20%–70%	20%–70%
Skin rashes	50%–70%	>90%
Morphology	Macule, papules, urticarial-like, petechia, purpura	Macule, papules, urticarial-like
BCG scar erythema	rare	30%–40%
Palmar/plantar edema and erythema	26%–68%	75%
Shock	40%–80%	2%–7%
Gastrointestinal symptom	60%–100%	20%
Dyspnea	19%–29%	Rare
Neurological symptom	13%–35%	5%–39%
Laboratory findings		
Lymphopenia	37%–81%	rare
Thrombocytopenia	11%–31%	Uncommon
Inflammatory markers	Increased ~100%	Increased ~100%
Increased troponin	33%–95%	rare
Increased proBNP	73%–95%	rare
Increased ferritin	54%–75%	rare
Increased D-dimer	91%–98%	rare
Sterile pyuria	50%	50%
Coronary artery dilatation	14%–48%	10%–30%
Mortality rate	1%–3%	<0.5%

BCG, *Bacillus Calmette-Guérin*; proBNP, pro-brain natriuretic peptide.

same continuum of the host immune response. They may share proximal pathways of immunopathogenesis. However, the immune responses diverge in other laboratory parameters and cardiac phenotypes.[61]

Several proposed mechanisms for the development of KD and KD shock syndrome include superantigen-mediated exaggerated inflammation, overproduction of proinflammatory cytokines, and involvement of gut bacteria.[9] Because of similar clinical presentations, the development of MIS-C may follow a similar pathway. Possible mechanisms for an autoimmune response triggered by SARS-CoV-2 infection include immune complex formation, antibody or T-cell recognition of self-antigens (molecular mimicry) or viral antigens expressed on infected cells.[9]

MIS-N may occur in children with infection of the mothers but not the neonates. Such an illness must be caused by transplacental transfer of maternal antibodies or other mediators.[43] If MIS-C and MIS-N share a common mechanism, MIS-C should also be induced by some humoral factors, especially autoantibodies.

The cell receptor of SARS-CoV-2 is angiotensin converting enzyme 2 (ACE2) receptor that is widely distributed in many organs, including heart, kidney, lung, and intestine.[62,63] It is also expressed in endothelial cells that is the underlying mechanism of diffuse vasculopathy observed in patients with severe COVID-19.[64,65] Evidences showed that SARS-CoV-2 may directly infected vascular endothelial cells and cardiomyocytes.[64–66]

Some patients with moderate to severe COVID-19 are associated with increased levels of autoantibodies,[67–69] including autoreactive antibody against vascular endothelial cells and cardiomyocytes.[70,71] Involvement of heart, intestine, lung, kidney, and vessels are the hallmark of MIS-C, while all these organs/systems can be infected directly by SARS-CoV-2 because of the abundance of ACE2 receptor expression. Autoantibody induced by viral antigen expressed on the surface of infected susceptible cells should be considered as one possible mechanism for the development of MIS-C.

The incidence of hypotension/shock is much lower than that of myocarditis in MIS-C.[14] This suggests that hypotension/shock observed in MIS-C may not be purely cardiogenic. It may be caused by a combined effect of cardiogenic, hypovolemia, and distributive hypotension. All these three factors should be put into consideration while managing such patients.[8]

Management

To date, there are no universally accepted guidelines for the management of MIS-C. In general, hospitalized patients

should receive fluid resuscitation, inotropic support, respiratory support, and extracorporeal membrane oxygenation in very severe cases.[9,72] Because clinical presentations of MIS-C are similar to severe bacterial infections, empiric use of broad-spectrum antibiotics are justified in severe cases.[8]

The hypotension in patients with MIS-C may be a mixed consequence of myocardial failure, decreased vascular tone, and volume depletion, fluid overload should be avoided to prevent worsening of myocardial failure. Because of myocardial failure, hypotension in patients with MIS-C may be fluid resistant. Inotropic agents should be used if necessary. Dobutamine or epinephrine may be used as the first-line treatment for children and norepinephrine may be added for refractory shock.[9]

Several studies suggested that intravenous immunoglobulin (IVIG) along may be less effective than IVIG plus steroid.[73–75] IVIG (2 gm/kg) and low-to-moderate dose of methylprednisolone (1–2 mg/kg/day) are usually recommended as the routine treatment to suppress the hyperinflammatory status of MIS-C.[72,76] The use of steroid is restricted to patients with diagnostic criteria of KD by the recommendation from WHO.[77] For patients with significant cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily for 2 days).[72] For MIS-C refractory to initial treatment, high-dose methylprednisolone (10–30 mg/kg/day) or high dose anakinra (5–10 mg/kg daily), or infliximab (5–10 mg/kg for 1 dose) may be used.[72,76] Immunomodulatory agents may be tapered for 2–3 weeks, or for longer period.[72]

Similar to the management of KD, low-dose aspirin (3–5 mg/kg/day) may be given routinely to patients with MIS-C.[72,76] Aspirin should be given for at least 4 weeks until the inflammatory markers normalized and the coronary artery has been shown to be normal.[72] Anticoagulants may be considered in patients with large coronary artery aneurysm, patients with moderate to severe left ventricular dysfunction, and patients with documented thrombosis.[72,76]

Prognosis

The prognosis of MIS-C is generally good. Most cases show resolution of inflammation and related symptoms within 1–4 weeks after the onset of illness.[8,38] Progression of coronary artery abnormalities may occur after discharge, suggesting possible long-term complications.[78] A 6-month follow-up study showed a significant proportion of patients has emotional difficulty, exercise intolerance and mild impairment of neurological functions.[79]

Reported mortality rate ranged between 1% and 3%, slightly higher than that for Kawasaki disease with current treatment recommendations (Table 3)8,24,29,38 Despite comorbid conditions are associated with a higher mortality in patients with COVID-19, most fatal cases of MIS-C do not have comorbidities.[7,12,13,38]

Prevention

In addition to non-pharmaceutical interventions, SARS-CoV-2 vaccines are shown to be protective against MIS-C. Protective effectiveness of vaccination is reported to be 91%–94%. Such an effectiveness is similar to protection of vaccine against moderate to severe COVID-19, and is higher than that against mild COVID-19.[80–82] Although several cases of MIS-C have been reported following SARS-CoV-2 vaccination,[83,84] these events may be attributed to concurrent SARS-CoV-2 infections and are not causally related to vaccination.

Perspectives

There are several unresolved issues related to MIS-C. The diagnostic criteria are different in different settings. The widely accepted criteria at present may miss some patients with mild or atypical MIS-C that share a common pathogenesis with classical MIS-C. The requirement of hospitalization in CDC criteria may ignore patients with mild MIS-C. The prerequisite for the presence of fever in both CDC and WHO criteria has not taken into account the possibility of afebrile MIS-C.[9,10,29] In contrast to MIS-C criteria that require 100% occurrence of fever, fever is present in only 18%–36% of children with MIS-N.[22,43] MIS-N is apparently a variant of MIS-C, and both disorders should share a common pathogenesis. With the strict diagnostic criteria, the true incidence of MIS-C may be underestimated.

MIS-C and KD share many common features, and are both a consequence of dysregulated, over-exaggerated inflammatory responses in genetically susceptible host. The presence of MIS-N suggest that MIS-C may be a result of autoreactive humoral immune response after COVID-19. Exploring the pathogenesis of MIC-C may help to understand the mysterious etiology and pathogenesis of KD.[8,20,21,47]

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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