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COVID-19 and multisystem inflammatory syndrome in children and adolescents

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As severe acute respiratory syndrome coronavirus 2 continues to spread worldwide, there have been increasing reports from Europe, North America, Asia, and Latin America describing children and adolescents with COVID-19-associated multisystem inflammatory conditions. However, the association between multisystem inflammatory syndrome in children and COVID-19 is still unknown. We review the epidemiology, causes, clinical features, and current treatment protocols for multisystem inflammatory syndrome in children and adolescents associated with COVID-19. We also discuss the possible underlying pathophysiological mechanisms for COVID-19-induced inflammatory processes, which can lead to organ damage in paediatric patients who are severely ill. These insights provide evidence for the need to develop a clear case definition and treatment protocol for this new condition and also shed light on future therapeutic interventions and the potential for vaccine development.

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For the French translation of the abstract see Online for appendix 1

For the Chinese translation of the abstract see Online for appendix 2

For the Arabic translation of the abstract see Online for appendix 3

For the Spanish translation of the abstract see Online for appendix 4

For the Russian translation of the abstract see Online for appendix 5

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Introduction

Since a cluster of pneumonia cases arising from unknown causes was first reported in Wuhan (Hubei province, China) in December, 2019, the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide. As of Aug 5, 2020, there are more than 18 million confirmed cases of COVID-19 and over 690 000 deaths.[1]

Children and adolescents make up a small proportion of COVID-19 cases. National statistics from countries in Asia, Europe, and North America show that paediatric cases account for 2·1–7·8% of confirmed COVID-19 cases.[2–5] However, because of asymptomatic infections, the underdiagnosis of clinically silent or mild cases (typically occurring in younger people), and the availability, validity, and targeted strategies of current testing methods (eg, viral testing instead of serological testing), there is still uncertainty about the actual disease burden among children and adolescents. Although the manifestations of the disease are generally milder in children than in adults, a small proportion of children require hospitalisation and intensive care.[6,7]

In the past 3 months, there have been increasing reports from Europe, North America, Asia, and Latin America describing children and adolescents with COVID-19-associated multisystem inflammatory conditions, which seem to develop after the infection rather than during the acute stage of COVID-19. The clinical features of these paediatric cases are both similar and distinct from other well described inflammatory syndromes in children, including Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome.[8–36] This COVID-19-associated multisystem inflammatory syndrome in children and adolescents is referred to interchangeably as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, and herein is referred to as MIS-C. MIS-C can lead to shock and multiple organ failure requiring intensive care. The European and US Centers for Disease Prevention and Control (CDC), Australian Government Department of Health, and WHO have released scientific briefs or advisories for MIS-C in response to this emerging challenge.[6,9,37,38]

Much remains unknown regarding the epidemiology, pathogenesis, clinical spectrum, and long-term outcomes of MIS-C. In this Review, we critically appraise and summarise the available evidence to provide insights into current clinical practice and implications for future research directions.

Case definitions and clinical spectrum

Different terminology and case definitions for this COVID-19-associated multisystem inflammatory phenotype in

Key messages

- Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children are generally mild and non-fatal, there is increasing recognition of a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, also known as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, herein referred to as MIS-C, which can lead to serious illness and long-term side-effects
- Clinical and laboratory features of MIS-C are similar to those of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome, but the disorder has some distinct features, and it needs a clear clinical and pathophysiological definition
- MIS-C might be distinct from Kawasaki disease, with features including an age at onset of more than 7 years, a higher proportion of African or Hispanic children affected, and diffuse cardiovascular involvement suggestive of a generalised immune-mediated disease
- Pathophysiology of MIS-C is still unclear and possible mechanisms include antibody or T-cell recognition of self-antigens (viral mimicry of the host) resulting in autoantibodies, antibody or T-cell recognition of viral antigens expressed on infected cells, formation of immune complexes which activate inflammation, and viral superantigen sequences which activate host immune cells
- Most cases of MIS-C associated with COVID-19 were managed following the standard protocols for Kawasaki disease, with inotropic or vasoactive agents often required in patients with cardiac dysfunction and hypotension and anticoagulation also used frequently; clinical research is required to prove the effectiveness and safety of these treatments
- The medium-term to long-term outcomes of MIS-C, such as the sequelae of coronary artery aneurysm formation, remain unknown and close follow-up is important

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children are used depending on the country and region. An internationally accepted case definition for MIS-C is still evolving. The UK has used PIMS-TS as their preliminary case definition for this disease, with criteria that include clinical manifestations (eg, persistent inflammation), organ dysfunction, SARS-CoV-2 PCR testing, which might be positive or negative, and exclusion of any other microbial cause.[9,39] The US CDC case definition is based on clinical presentation, evidence of severe illness and multisystem (two or more) organ involvement, no plausible alternative diagnoses, and a positive test for current or recent SARS-CoV-2 infection or COVID-19 exposure within 4 weeks before the onset of symptoms.[37] WHO has developed a similar preliminary case definition and a case report form for multisystem inflammatory disorder in children and adolescents. This case definition for MIS-C includes clinical presentation, elevated markers of inflammation, evidence of infection or contact with patients who have COVID-19, and exclusion of other obvious microbial causes of inflammation (table 1).[6]

Cases reported in the past 3 months, which met the current diagnostic criteria, most likely represent a small proportion of MIS-C cases, and those individuals were severely affected by the illness. A broader UK definition of MIS-C describes this illness as a spectrum ranging from persistent fever and inflammation, to characteristic features of Kawasaki disease in children, and to children who are severely ill with shock and multiple organ failure.[39,40] In the study by Dufort and colleagues,[21] a third of the reported cases did not meet the US CDC case definition for MIS-C but presented with similar clinical and laboratory features to those seen in confirmed cases.

Despite overlap in clinical presentation, the initially speculated relationship between MIS-C and toxic shock syndrome seems implausible because most MIS-C cases had negative blood cultures (appendix 6 pp 3–4); thus, there is no evidence that staphylococcal or streptococcal toxins are involved in the cause of MIS-C. However, studies to exclude infection with superantigen-producing organisms are scarce. Overlap has also been observed between

	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19	Complete Kawasaki disease	Incomplete Kawasaki disease	Kawasaki disease shock syndrome
Organisation or publication	WHO[6]	Royal College of Pediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]	American Heart Association[40]	American Heart Association[40]	Kanegaye et al,[41]
Age	0–19 years	Child (age not specified)	<21 years	Child (age not specified)	Child (age not specified)	Child (age not specified)
Inflammation	Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers	Fever lasting 5 days or more*	Fever lasting 5 days or more*	Fever
Main features	Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (appendix 6 pp 3–4)	Clinically severe illness requiring hospitalisation; and multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)	Four or more principal clinical features: (A) erythema and cracking of lips, strawberry tongue or oral and pharyngeal mucosa; (B) bilateral bulbar conjunctival injection without exudate; (C) rash; (D) erythema and oedema of the hands and feet in acute phase and periungual desquamation in subacute phase; and (E) cervical lymphadenopathy	Two or three principal clinical features or a positive echocardiogram	Kawasaki disease-like clinical features and any of the following causing initiation of volume expansion, vasoactive agents, or transfer to the intensive care unit: systolic hypotension based on age, or a decrease in systolic blood pressure from baseline by 20% or more, or clinical signs of poor perfusion
Exclusion	Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses	..	..	Other microbial cause
SARS-CoV-2 status	Positive RT-PCR, antigen test, or serology; or any contact with patients with COVID-19	RT-PCR positive or negative	Positive RT-PCR, serology, or antigen test; or COVID-19 exposure within the past 4 weeks before symptom onset	..	..	..

MIS-C=multisystem inflammatory syndrome in children. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *In the presence of four or more principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of Kawasaki disease can be made with only 4 days of fever.

Table 1: **Preliminary case definitions for MIS-C**

the diagnostic criteria of Kawasaki disease, Kawasaki disease shock syndrome, and the newly emerged MIS-C. According to criteria developed by the American Heart Association,[42] the diagnosis of complete Kawasaki disease includes the presence of a high fever for 5 days or more and at least four of the five principle clinical features, whereas incomplete Kawasaki disease is diagnosed when children present with unexplained fever for 5 days or more and two to three of the principle clinical features supported by laboratory findings or cardiac lesions (table 1).

Kawasaki disease shock syndrome is a severe form of Kawasaki disease,[41] defined as complete or incomplete Kawasaki disease complicated by haemodynamic instability, resulting in the patient requiring intensive care, without evidence of another bacterial infection such as group A streptococcus or staphylococcus. The cause and factors contributing to the development of Kawasaki disease shock syndrome are still unclear, but a contributory role for underlying inflammation and more intense vasculitis has been suggested on the basis of laboratory results, progression, and the disease outcome.[43–47] Researchers have suggested several possible explanations for Kawasaki disease shock syndrome including a superantigen-mediated response,[48] overexpression of proinflammatory cytokines,[49] and gut bacteria involvement.[50] A large number of MIS-C cases present with Kawasaki-like clinical symptoms, and cardiac impairment and shock similar to Kawasaki disease shock syndrome. Gastrointestinal symptoms, hyponatremia, hypoalbuminemia, and intravenous immunoglobulin resistance are also common in Kawasaki disease shock syndrome and MIS-C (appendix 6 pp 3–4).

Although features of MIS-C overlap with those of Kawasaki disease, a study from Whittaker and colleagues[18] found a wider spectrum of MIS-C symptoms. Despite differences in severity, coronary aneurysms have occurred in all three groups of patients, including those with shock, those who meet the criteria for Kawasaki disease, and those with fever and inflammation but who do not have shock or meet the criteria for Kawasaki disease. In addition to a wider clinical spectrum, there are several other distinct features of MIS-C compared with Kawasaki disease, including the age and ethnic groups affected. Patients with MIS-C are typically older than 7 years, of African or Hispanic origin, and show greater elevation of inflammatory markers.[10,13,15,18] Over 80% of patients with MIS-C also present with an unusual cardiac injury shown by high concentrations of troponin and brain natriuretic peptide, whereas others develop arrhythmia, left ventricle dysfunction, and unusual coronary dilatation or aneurysms (appendix 6 pp 3–4).[10,12,13,15–19]

Blondiaux and colleagues[28] examined cardiac MRI findings in four patients who had MIS-C with cardiovascular involvement, and found a diffuse myocardial oedema on T2-weighted short-tau inversion recovery sequences and native T1 mapping, with no evidence of late gadolinium enhancement suggestive of replacement fibrosis or focal necrosis. These findings favour the hypothesis of an immune response to an antigen rather than a direct complication secondary to SARS-CoV-2 infection.

COVID-19 causes and link with MIS-C

Risk factors for developing severe disease among children infected with SARS-CoV-2 include age, viral load, and chronic comorbidities.[51–53] There is a U-shaped curve of severity in children diagnosed with COVID-19, and babies younger than 1 year are at a higher risk of developing severe COVID-19,[54] although these infections are infrequent. After the first year of life, most younger patients appear to be asymptomatic or have milder symptoms of SARS-CoV-2 infection.[4,55,56] Data suggest a genetic locus is partly associated with more severe disease,[57] and some ethnic groups (eg, African) might have a strong association with MIS-C.[13,31,33]

The relationship between coronaviruses and multisystem inflammatory diseases, such as Kawasaki disease, has been studied previously. Kawasaki disease is a systemic vasculitis in children and one of the leading causes of childhood-acquired heart disease.[58] Although its exact cause remains unknown, Kawasaki disease is thought to be triggered by a response to an infectious agent in genetically predisposed individuals, and research has focused on identifying host factors and specific triggers associated with the development of Kawasaki disease. Coronaviruses have a large genome, which might explain the varied pathogenicity and ability to affect multiple organs. In 2005, Esper and colleagues[59] reported a possible association of the New Haven coronavirus (previously identified as HCoV-NL63) with Kawasaki disease. However, five subsequent studies[60–64] showed negative results for this association. The results from newer studies remain inconclusive.[65–67] A South Korean study[65] from 2012, did not find a significant association between coronavirus strains OC43, 229E, and NL63 and Kawasaki disease. However, a Japanese study[66] published in 2014 found possible involvement of strain 229E in Kawasaki disease, but not strain NL63. Another South Korean study[67] from 2014 showed a non-significant correlation between monthly Kawasaki disease occurrence and monthly coronavirus infection.

In the current COVID-19 pandemic, there have been increasing observations of an inflammatory illness occurring in children; most reports were 4–6 weeks after the peak of COVID-19 infections in the affected population.[22,68] On April 7, 2020, Jones and colleagues[8] first reported a case of a 6-month-old infant in the USA, presenting with persistent fever and minor respiratory symptoms, who was diagnosed with Kawasaki disease and had a positive RT-PCR result for SARS-CoV-2. On April 24, 2020, the UK National Health Service had issued an alert on an emerging paediatric inflammatory multisystem disorder. On May 1, 2020, the UK Royal College of Paediatrics and Child Health published guidance[39] on the

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See **Online** for appendix 6

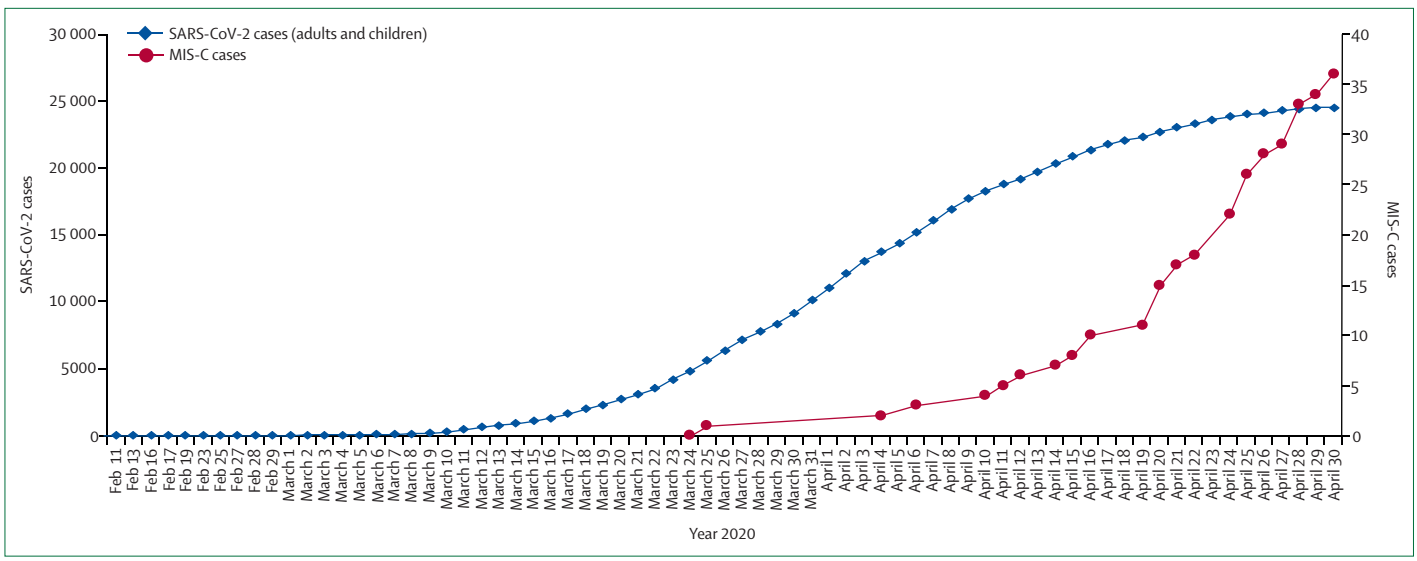

Figure 1: **Time course of MIS-C in PCR-positive COVID-19 cases**
Only incudes PCR-positive cases in London, UK. Data taken from Public Health England.[89] Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in children. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

clinical management of children with MIS-C and proposed a case definition. Since then, several other countries have reported that the multisystem inflammatory disease temporally associated with SARS-CoV-2 infection (appendix 6 pp 1–2).

COVID-19 pathophysiology and link with MIS-C

Coronaviruses are a large family of positive-sense single-stranded RNA viruses. There are four described genera of coronaviruses (α, β, δ, and γ).[69] Six species of human coronaviruses are known, with one species subdivided into two different strains. The β coronavirus genus includes SARS-CoV, SARS-CoV-2, and Middle East respiratory syndrome. SARS-CoV-2, similarly to other coronaviruses, is transmitted between humans primarily through close contact with the infected individual or through contaminated surfaces—eg, dispersing droplets when coughing or sneezing. The virus enters a cell mainly by binding to the angiotensin-converting enzyme 2, which is highly expressed in lung cells, alveolar cells, cardiac myocytes, the vascular endothelium, and a small subset of immune cells.[70–74] The pathogenesis of COVID-19 is still being studied. Evidence has shown that a dysregulated innate immune response and a subsequent cytokine storm,[70,74–80] and endothelial damage,[81,82] might play a role in the clinical manifestation of severe COVID-19 cases, leading to acute lung injury, acute respiratory distress syndrome, and multiple organ failure.

Neutrophils play a major role in the innate immune response. One of their functional mechanisms is the formation of neutrophil extracellular traps (NETs).[83] NETs are a lattice-like web of cell-free DNA, histones, and neutrophil granule content including microbicidal proteins and enzymes. NETs have been involved in the pathophysiology of a wide range of inflammatory and prothrombotic states such as sepsis, thrombosis, and respiratory failure. The generation of NETs by neutrophils, called NETosis, can be stimulated by many viruses. Although their major function is to trap the virus, virus-induced NETs can trigger inflammatory and immunological reactions in an uncontrolled manner, leading to an exaggerated systemic inflammatory response,[84] similar to hyperinflammation seen in MIS-C. Zuo and colleagues[85] have shown that NETs are increased in the plasma of patients infected with SARS-CoV-2, and higher concentrations of NETs are seen in those with respiratory failure. Thrombotic complications have been reported in severe COVID-19 cases. Abnormal coagulopathy (eg, elevated D-dimer or fibrinogen) has also been observed in many cases of MIS-C. NETosis plays a crucial part in promoting thrombosis;[86–88] therefore, the role of NETs in MIS-C is highly plausible. Although NETosis might be an important mechanism linking neutrophil activation, cytokine release, and thrombosis in COVID-19, they have not yet been reported to be involved in MIS-C.

Children form only a small portion of confirmed COVID-19 cases. Most children have had minor symptoms or an asymptomatic SARS-CoV-2 infection.[4,55,56] Unlike in adults, severe respiratory illness such as acute respiratory distress syndrome is rare in children. The newly emerging MIS-C might lead to severe clinical manifestations; however, its distinct characteristics are different from other severe complications seen in paediatric COVID-19 cases. First, MIS-C cases start appearing around 1 month after a COVID-19 peak in the population. According to data from Public Health England, the number of MIS-C cases increased drastically around April 16, 2020, approximately 4 weeks after the substantial increase in COVID-19 cases in

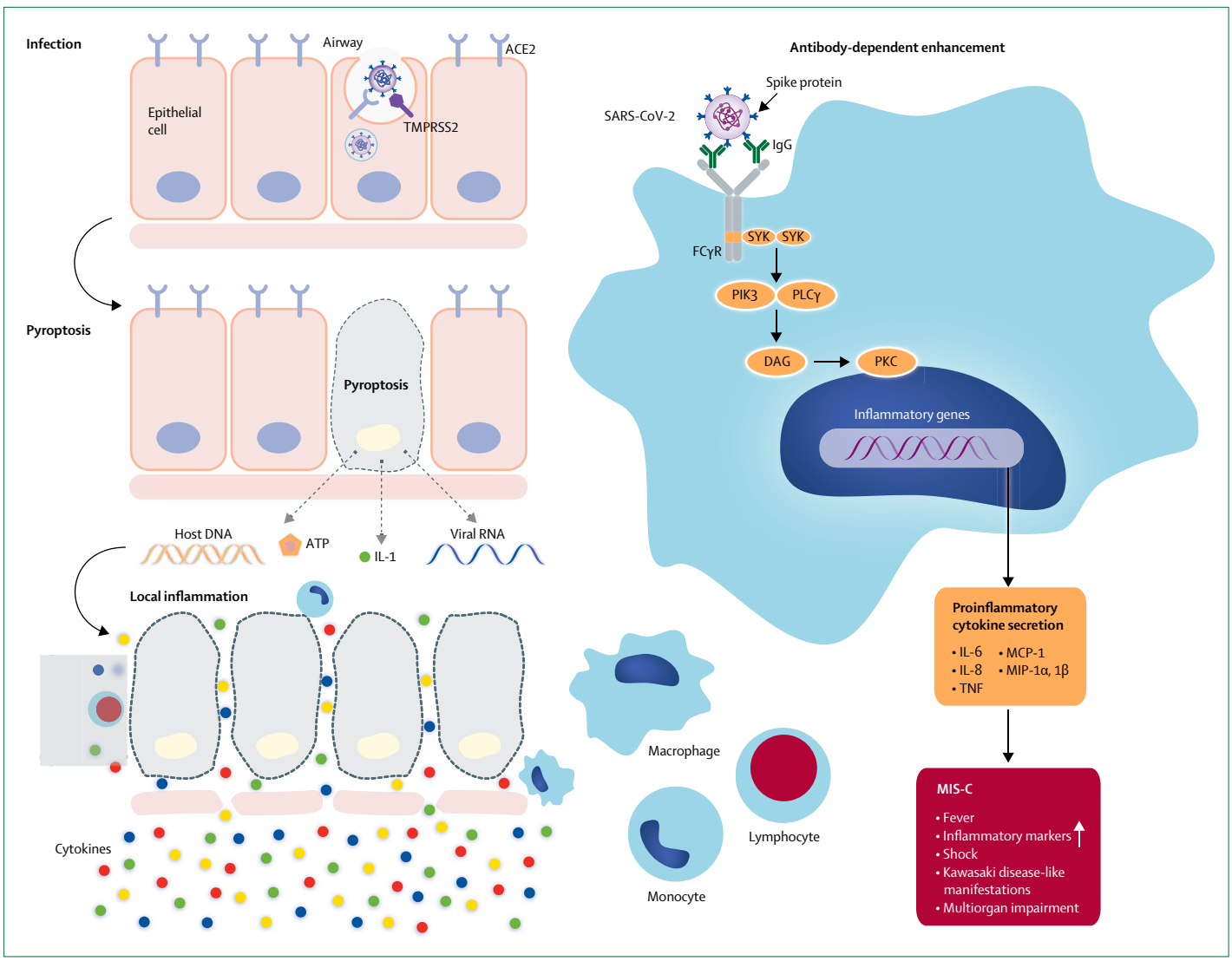

Figure 2: **Possible mechanisms of inflammatory processes for MIS-C**
Antibodies might enhance disease by increasing viral entry into cells. Alternative mechanisms include antibody or T-cell-mediated cell damage or activation of inflammation. Antibodies or T cells attack cells expressing viral antigens or attack host antigens which cross-react or mimic viral antigens. The low rate of virus detection in MIS-C would favour this second mechanism rather than the classic antibody-dependent enhancement. ACE2=angiotensin-converting enzyme 2. DAG=diacylglycerol. FcγR=Fc-gamma receptor. IL=interleukin. MCP=monocyte chemoattractant protein. MIS-C=multisystem inflammatory syndrome in children. MIP=macrophage inflammatory protein. PIK3=phosphoinositide 3 kinase. PKC=protein kinase C. PLCγ=phospholipase C gamma. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SYK=tyrosine protein kinase SYK. TMPRSS2=transmembrane serine protease 2. TNF=tumour necrosis factor.

the UK (figure 1).[89] Epidemiological studies from the USA[22] and France[68] revealed similar trends. Second, children often show previous rather than a current infection with SARS-CoV-2. Only a third of reported MIS-C cases are positive by RT-PCR for SARS-CoV-2, whereas most cases are positive with an antibody test, indicating past infection. The delay in presentation of this condition relative to the pandemic curve, a low proportion of cases who were SARS-CoV-2 positive by RT-PCR, and a high proportion who were antibody positive suggest that this inflammatory syndrome is not mediated by direct viral invasion but coincides with the development of acquired immune responses to SARS-CoV-2.

Selva and colleagues[90] compared the antibodies produced by children and adults against coronavirus proteins and found marked differences between the antibody responses in patients with COVID-19. The varying responses were linked to different Fcγ receptor binding properties and antibody subgroup concentrations. Although studies in patients with MIS-C are needed, these research findings suggest that differences in antibody response might contribute to the hyperinflammatory response seen in adults with COVID-19. Considering the similarities between the adult hyperinflammatory response and MIS-C, antibodies might play a role in both conditions. In a preprint study, Gruber and colleagues[91] have reported that

	Royal College of Paediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	..
Antibiotics for sepsis	..	Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	..

Table 2: **Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19**

patients with MIS-C had neutralising antibodies against SARS-CoV-2, which are associated with interleukin-18 (IL-18) and IL-16 activation, myeloid chemotaxis, and activation of lymphocytes, monocytes, and natural killer cells. Upregulation of the intercellular adhesion molecule 1 and Fc-γ receptor 1 on neutrophils and macrophages suggests enhanced antigen presentation and Fc-mediated responses. Gruber and colleagues[91] also reported the presence of autoantibodies against endothelial, gastrointestinal, and immune cells in patients with MIS-C.

Antibodies to SARS-CoV might accentuate disease through antibody-dependent enhancement of viral entry and amplification of viral replication, as observed in dengue,[92–94] or by triggering a host inflammatory response through the formation of immune complexes or direct anti-tissue antibody activation or cellular activation, or both. Similar mechanisms might be involved in the inflammatory disorder associated with SARS-CoV-2. SARS-CoV-2 is not usually detected in patients with MIS-C; thus the antibody-dependent enhancement of inflammation is more likely to occur through an acquired immune response rather than increased viral replication. Anti-spike antibodies against SARS-CoV have been shown to accentuate inflammation in primates and in human macrophages;[95] therefore, the anti-spike antibodies against SARS-CoV-2 might also be able to trigger inflammation through a similar mechanism (figure 2). Hoepel and colleagues[96] have reported, in a preprint study, that immune complexes generated by linking patient anti-spike antibodies with spike protein cause macrophage activation, which supports the proposed mechanism for SARS-CoV-2.

The inflammatory disorders triggered by SARS-CoV-2 have features similar to Kawasaki disease and can also result in coronary aneurysms. This finding suggests that the virus might be acting as the immune trigger and causing a similar immune-mediated injury to the heart and coronary arteries as the one seen in Kawasaki disease. Immune complexes have been well documented in Kawasaki disease,[97–100] and might mediate vascular injury by activation of inflammatory responses through the Fc-γ receptor or complement activation. This theory is supported by the fact that genetic variants associated with Kawasaki disease include *FCGR2A*, B-lymphoid tyrosine kinase, and the CD40 ligand gene,[101–103] which are genes involved in antibody production or clearance of immune complexes. The development of T-cell responses to SARS-CoV-2 might also play a role in organ damage and inflammatory processes since increased T-cell responses were seen in Kawasaki disease. Genetic variants in the inositol 1,4,5-triphosphate 3-kinase C (*ITPKC*) gene, regulating T-cell activation,[104] are associated with increased susceptibility to Kawasaki disease, and treatment with cyclosporin, which works by lowering T-cell activity, might have beneficial effects in the treatment of Kawasaki disease.[105]

The possible mechanisms for an acquired immune response to accentuate SARS-CoV-2 include: (1) antibody or T-cell recognition of self-antigens (viral mimicry of the host) resulting in autoantibodies; (2) antibody or T-cell recognition of viral antigens expressed on infected cells; (3) formation of immune complexes which activate inflammation; and (4) viral superantigen sequences which activate host immune cells.[106]

Management of MIS-C

To date, there are no widely accepted guidelines on the management of MIS-C, but several organisations have published their own guidelines (table 2). Physicians at various centres have created treatment protocols based on specific symptoms, previous treatment of similar conditions such as Kawasaki disease, or COVID-19 treatment guidelines for adult patients. If MIS-C is suspected or diagnosed, a multidisciplinary team approach should be taken, including a paediatric infectious diseases unit, and cardiology, immunology, rheumatology, and intensive care unit teams to consider antiviral therapy (if PCR positive for SARS-CoV-2) or immunotherapy, or both. General

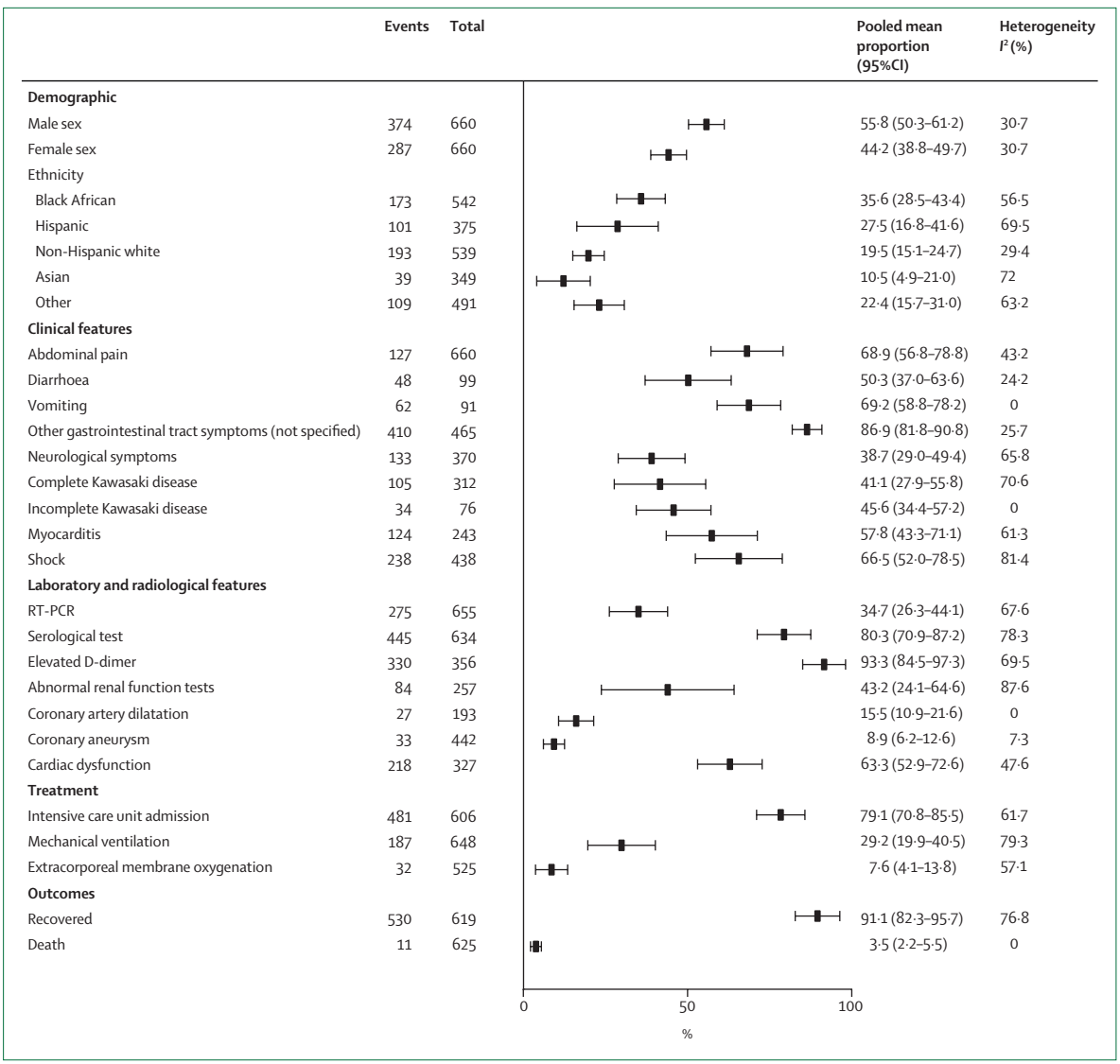

Figure 3: **Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with COVID-19[8–36]**
Three case series were not included in the meta-analysis because of the overlap in cases. Cases reported in two studies[34,35] were also included in the case series reported by Feldstein and colleagues.[22] Cases reported by Riphagen and colleagues[10] were also included in the study by Whittaker and colleagues.[18] The random-effect model is applied.

supportive care is crucial, especially attention to vital signs, hydration, electrolytes, and metabolic status. Few children present with respiratory compromise or hypoxia, but they should be closely monitored for potential compromise.

Standard protocol for Kawasaki disease

Because many cases met the diagnostic criteria of classic or incomplete Kawasaki disease, most reported MIS-C cases were treated using the standard protocol for Kawasaki disease, which is intravenous immunoglobulin with or without aspirin (appendix 6 pp 3–4).[8–36,107,108] A large proportion of MIS-C cases (67%) have a similar presentation to Kawasaki disease shock syndrome, mainly shock, so supportive and inotropic or vasoactive treatment should also be applied. Steroids have also been used to treat MIS-C. Because clinical and laboratory features of MIS-C overlap with those of Kawasaki disease, Kawasaki disease shock syndrome, and macrophage activation syndromes, patients with severe MIS-C have received immunomodulatory agents such as infliximab (anti-tumour necrosis factor drug),[18,25] tocilizumab (IL-6 antagonist),[16,17,22,24,25] and anakinra (IL-1 receptor antagonist),[15,17,18,20,22,24–27] which have been shown to be effective in similar diseases. There is no consensus on which of these agents is optimal, and the choice of drug is dependent on clinician preference, cytokine panel results, and availability. Randomised clinical trials are needed to establish which treatment is beneficial and

effective at preventing or reversing shock and cardiac failure, or the development of coronary artery aneurysms. However, because clinical trials take a long time to complete, an international best available treatment study[109] has been initiated. This study will invite paediatricians to collaborate globally and provide information on the treatment administered to children with inflammatory diseases temporally associated with COVID-19. Propensity score matching will be used to compare the rate of inflammation resolution with other outcomes such as length of hospital stay, overall survival, and frequency and severity of coronary artery aneurysms, which will help to inform the design of randomised trials.

The role of remdesivir and dexamethasone

Remdesivir is a nucleoside analogue that inhibits the action of viral RNA polymerase resulting in the termination of RNA transcription, which decreases viral RNA production and has been shown to shorten COVID-19 illness duration in adults.[110] However, because remdesivir inhibits the actively replicating virus and most children with MIS-C are not in the acute phase of illness and the virus is not detectable by PCR, the role of remdesivir in the treatment of MIS-C is limited. In rare cases in which the PCR test is positive and the child is severely ill, the use of remdesivir could be considered.

The recent UK RECOVERY trial,[111] has shown that dexamethasone might reduce death by a third in patients who are on mechanical ventilation as a result of severe respiratory complications from COVID-19. In line with these new findings, administration of low-dose dexamethasone to patients with MIS-C could be beneficial to suppress the immune response and subsequent inflammatory disorders. Other steroids such as methylprednisolone or prednisolone have become extensively used for MIS-C; thus, prospective clinical trials are needed to identify the role of steroids, the optimal dose, and the appropriate agent.

Treatment for children with hypotension

Many children with MIS-C also present with hypotension. If signs of shock are present, patients should be resuscitated with volume expansion using buffered or balanced crystalloids[112] (ie, Plasma-Lyte B or Ringers lactate) and patients should stay under close monitoring. Hypotension in children with MIS-C is often fluid resistant and vasopressors should be added if necessary. Epinephrine is recommended as the first-line treatment for children and norepinephrine is added if the shock persists. Using dobutamine has also been suggested in patients with severe myocardial dysfunction, because of its selective inotropic effect.[17,113] Because some patients might have severe myocardial dysfunction, caution is needed to avoid fluid overload. Initiation of broad-spectrum antibiotics is also appropriate because the clinical presentation (eg, high C-reactive protein, increased neutrophils) makes it difficult to exclude bacterial infection; however, antibiotic treatment should be stopped once the infection has been excluded and the patient is improving. Most children with MIS-C do not require respiratory support for pulmonary disease; however, some children have required intubation and extracorporeal membrane oxygenation as a result of cardiovascular collapse.[10,15–17]

Cardiac monitoring and follow-up

The first animal model to support the hypothesis that viruses belonging to the coronavirus family were able to induce acute myocarditis and congestive heart failure was shown in a study in 1992.[114] The heart also appears to be a major target of injury in MIS-C. Many patients present with significantly elevated troponin (80·9%, 95% CI 70·2–88·4) or brain natriuretic peptide (84·9%, 77·3–90·3), or both, which indicates myocardial cell injury, and some patients also develop arrhythmia and left ventricle dysfunction (63·3%, 52·9–72·6).[10,12,13,15–19] Coronary artery dilatation was observed in 8·9% (95% CI 6·2–12·6) of patients, whereas aneurysm formation was seen in 15·5% (10·9–21·6) of patients at presentation (figure 3, appendix 6 pp 3–4), and a smaller proportion have shown persistent coronary artery aneurysms at discharge from hospital.[8,10,12,13,15,17–19] The incidence of coronary artery aneurysms that might develop after discharge from hospital is unknown. Arrhythmia, myocardial injury, or conduction injury have also been detected by an electrocardiogram in some cases of MIS-C.[17,18] Coronary artery aneurysms have not only been reported in children with severe MIS-C and those with Kawasaki disease, but also in children showing only fever and inflammation;[18] therefore, cardiac assessment and follow-up is essential in all cases. All patients need echocardiographic assessment on presentation and daily electrocardiogram monitoring in severe cases. To establish if coronary artery injury has occurred, follow-up echocardiograms are needed at discharge from hospital and after 2–6 weeks. A cardiac MRI assessment should be considered to investigate whether persistent myocardial damage was induced by a viral infection or mediated by a cytokine storm.[115–118] However, a cardiac MRI is difficult and time-consuming, especially when young patients are intubated. Given that there are many unknowns about the long-term cardiovascular morbidity in children with MIS-C, a cardiology follow-up is recommended for all cases.

Coagulopathy prevention and management

A hallmark of COVID-19 in adult and paediatric patients has been the striking coagulopathy. Some patients have developed major vessel thrombosis. Although mechanisms underlying the coagulopathy in COVID-19 are still unknown, anticoagulant therapy (mainly heparin or low-molecular-weight heparin) is currently recommended for patients with severe COVID-19.[17–19,56] Many children with

MIS-C have elevated D-dimers which, in some institutions, is used as a guide for giving anticoagulants, especially for those with a high concentration of D-dimers. Overall, there is substantial variability and a lack of consensus on anticoagulants. Low-dose aspirin, used in Kawasaki disease, has also been used for MIS-C. In patients who are severely ill with COVID-19-associated inflammatory syndrome and with marked inflammation, raised D-dimers, and a high fibrinogen concentration, anticoagulation therapy and antiplatelet therapy are generally recommended depending on the risk of thrombosis in adults. Dose, duration, and the choice of anticoagulants should be decided during consultation with paediatric haematologists and should be closely monitored throughout the illness. Low-dose aspirin is given until the follow-up echocardiograms exclude persisting coronary artery aneurysms or injury. Further research is needed on the mechanisms and treatment of coagulopathy in COVID-19.

Follow-up after discharge from hospital

Paediatric patients diagnosed with MIS-C often require special care and aggressive treatment; however, most patients have shown favourable outcomes (appendix 6 pp 1–2). Children can be discharged from hospital once their inflammatory laboratory markers have normalised; they are afebrile, normotensive, and well hydrated; and they do not require supplementary oxygen. Close follow-up is very important because the natural history of MIS-C is still unclear; in most centres the follow-up occurs with the child's primary care provider and subspecialists from infectious diseases, rheumatology, cardiology, and haematology. The medium-term to long-term outcomes, such as the sequelae of coronary artery aneurysm formation following MIS-C, remain unknown and represent an important area of future research.

Treatment choices for resource-limited countries

Cases of MIS-C have also been reported in low-income and middle-income countries (LMICs).[11,14] Because many therapeutic agents used to treat MIS-C are unavailable or unaffordable in most LMICs, the choices for immunomodulation are limited. Steroids are a cheap and more accessible option in LMICs, but their potential to induce broad immunosuppression might be hazardous in countries in which tuberculosis and HIV infection are highly prevalent and where diagnostic facilities (to exclude other types of infection) are scarce. Therefore, steroid use needs to be restricted to short-term courses in children who have been hospitalised with MIS-C and who are severely ill. Trials to establish the optimal treatment in high-income countries, that would also include agents which are available and affordable in LMICs, are needed. The ongoing international study comparing the best available treatment depending on clinician preference and drug availability,[109] might provide information on the treatment options available in LMICs.

Conclusion

SARS-CoV-2 is a novel virus, and currently only scarce scientific evidence is available to understand its association with multisystem inflammatory syndrome in paediatric patients. Although there has been an increasing number of case reports and case series, the global and population-specific incidence of MIS-C remains unknown, and the causal relationship and pathogenesis of Kawasaki disease and MIS-C remain unclear. Although there is some evidence that the development of MIS-C is a post-viral immunological reaction to COVID-19, understanding of the immune response induced by SARS-CoV-2 remains poor.

There are many questions currently emerging that need to be answered—for example, how the pathophysiology of MIS-C differs from Kawasaki disease, Kawasaki disease shock syndrome, toxic shock syndrome, and macrophage activation syndromes. Genetic factors are well recognised contributors to Kawasaki disease susceptibility, but it is unknown whether the same or different genetic factors influence MIS-C. Another question is whether patients with fever and inflammation following SARS-CoV-2 infection progress to Kawasaki disease, shock, or organ failure if left untreated. Clinical trials are needed to establish which treatment is optimal and could possibly reverse inflammatory processes and prevent coronary artery aneurysms. Other emerging questions include: whether infection at a different stage of childhood and adolescence influences the severity of disease progression and prognosis; whether there are differences in clinical features or underlying immunology of MIS-C when further stratified by age (neonates, children, and adolescents); and whether MIS-C is associated with an increased risk of medium-term to long-term adverse paediatric outcomes. Importantly, future trials need to investigate whether the pathophysiology and mechanisms for the immune response of MIS-C will help to inform the development of safe and effective SARS-CoV-2 vaccines for use in children.

As the COVID-19 outbreak evolves, the scientific community needs to generate good evidence for the diagnosis and treatment of MIS-C. A recent report[119] from the US CDC describes in detail the clinical characteristics and treatment modalities available for patients with MIS-C in a large case series of the US population. However, epidemiological data using cohort or case-control designs are urgently needed to establish the cause and causality between COVID-19 and MIS-C. Clinical management and potential treatment protocols should be tested in randomised controlled trials or cohort designs to compare clinical outcomes and changes in inflammatory markers. It is also important to understand whether Kawasaki disease-type morbidities, including coronary artery dilatation, occur in patients with MIS-C and how frequently they occur, and whether the use of aspirin or other interventions can reduce this risk and long-term morbidities. Laboratory investigations into the pathophysiological and immunological mechanisms of the disease are urgently

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 1985, to July 7, 2020, using the Medical Subject Headings terms "SARS virus", "coronavirus", "systemic inflammatory response syndrome", "mucocutaneous lymph node syndrome (Kawasaki disease)", "infant, newborn", "child", "adolescent", and any relevant entry terms and supplementary concepts. Relevant articles and data were also identified through searches in Google Scholar, WHO, Centers for Disease Control and Prevention, UK National Health Service, and other websites. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English were identified and included.

needed to provide insights into potential treatment targets and to inform strategies for vaccine development. Finally, with the small number of cases globally, establishing an international research collaboration is vital to rapidly conduct these studies in a coordinated and effective way.

Contributors

ZAB is the guarantor. ZAB conceptualised the paper and established the writing consortium. LJ, KT, and OI developed the first draft under supervision by ZAB. ML wrote the sections on pathophysiology and diagnosis. LJ, KT, ML, OI, SKM, KW, JDK, and ZAB contributed to the writing and the review process.

Declaration of interests

We declare no competing interests.

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