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REVIEW

Severe acute respiratory syndrome coronavirus 2-related multisystem inflammatory syndrome in children mimicking Kawasaki disease

Syndrome multi-systémique inflammatoire lié au SARS-CoV-2 chez l'enfant mimant un syndrome de Kawasaki

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Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; IL, interleukin; IQR, interquartile range; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; PICU, paediatric intensive care unit; PIMS-TS, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSS, toxic shock syndrome.

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Cardiogenic shock;
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Summary The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been characterized by high transmission rates and high mortality in adults with predisposing factors, including age > 70 years, obesity, diabetes, systemic hypertension and other underlying diseases. During the second week of viral pneumonia, acute respiratory distress syndrome can occur and carries high mortality. Unlike most common respiratory viruses, children seem to be less susceptible to SARS-CoV-2 infection, and generally develop mild disease with low mortality. However, clusters of severe shock associated with high levels of cardiac biomarkers and unusual vasoplegia requiring inotropes, vasopressors and volume loading have recently been described. Both the clinical symptoms (i.e. high and persistent fever, gastrointestinal disorders, skin rash, conjunctival injection and dry cracked lips) and the biological signs (e.g. elevated C-reactive protein/procalcitonin and high levels of ferritinaemia) mimicked Kawasaki disease. In most cases, intravenous immunoglobulin therapy improved cardiac function and led to full recovery within a few days. Adjunctive steroid therapy and sometimes biotherapy (e.g. anti-interleukin 1Ra and anti-interleukin 6 monoclonal antibodies) were often necessary. Although almost all children fully recovered within a week, some of them later developed coronary artery dilation or aneurysm. Thus, a new “multisystem inflammatory syndrome in children” related to SARS-CoV-2 has recently been described. Similarities with Kawasaki disease and the physiopathology of this syndrome still need further exploration.

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MOTS CLÉS

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Résumé La pandémie due à SARS-CoV-2 est caractérisée par une haute contagiosité et une mortalité élevée chez les adultes à risque (âge supérieur à 70 ans, obésité, diabète, hypertension, autres pathologies associées). Au décours d'une pneumonie virale, peut survenir une phase hyper-inflammatoire compliquée d'une défaillance multi-viscérale avec Syndrome de Détresse Respiratoire Aiguë. Contrairement à la majorité des virus respiratoires, les enfants apparaissent moins susceptibles à SARS-CoV-2 et développent généralement une forme peu sévère, avec une faible mortalité. Cependant, des cas groupés d'états de choc associés à des biomarqueurs cardiaques élevés et à une vasoplégie inhabituelle nécessitant un traitement par inotropes, vasopresseurs et un remplissage vasculaire ont été récemment décrits. Les symptômes cliniques observés (fièvre élevée et durable, troubles digestifs, rash cutané, injection conjonctivale, chéleite) et le profil biologique (CRP/PCT élevées, hyperferritinémie) évoquent un syndrome de Kawasaki qui répond à un traitement par perfusion intraveineuse d'immunoglobulines complété si besoin par une corticothérapie et/ou une biothérapie anti-interleukine 1Ra ou anti-interleukine 6. La majorité des enfants guérit en quelques jours avec cependant une possible dilatation des artères coronaires. Ainsi, un nouveau syndrome inflammatoire multi-systémique associé à SARS-CoV-2 mimant un syndrome de Kawasaki a été récemment identifié chez l'enfant et questionne sur sa physiopathologie proche ou dissemblable de ce syndrome d'étiologie restée jusqu'ici inconnue.

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Background

While the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was spreading worldwide, with more than 130 million people infected by April 2021 and a death toll of more than 2.7 million people, children accounted for only a small fraction (0.2%) of infected patients [1]. Most of the time these children presented with mild symptoms of viral upper and/or lower respiratory tract infection, including short-lasting fever, dry cough, fatigue, myalgias and/or cephalalgia requiring, in the worst cases, low-flow oxygen therapy and a few days of hospitalization [2]. Mortality rates were low, ranging from 0.02% in 5015 children with mild

disease to 2% in 319 children with severe disease and/or underlying chronic diseases, including obesity [3].

However, clusters of children developing “cardiogenic shock” (i.e. shock associated with low left ventricular ejection fraction and elevated cardiac biomarkers) together with unusually low diastolic pressure suggestive of associated “toxic shock” [4] and other features similar to Kawasaki disease (KD) (high fever, cutaneous rash and conjunctival injection) were described in England, Italy, France and the USA. Two facts were particularly striking: (1) this new syndrome—called either “paediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2” (PIMS-TS) in the UK or “multisystem inflammatory syndrome

in children” (MIS-C) in the USA—occurred 2 to 4 weeks after an episode of SARS-CoV-2 infection; and (2) the syndrome included high levels of inflammatory markers, such as C-reactive protein, ferritin and D-dimers, highly suggestive of “cytokine storming” [5]. Although inotropes or vasopressors were initially prescribed in most cases, hypotension was often responsive to fluid resuscitation. Furthermore, cardiac function improved rapidly after intravenous immunoglobulins (IGIVs) and often steroids and sometimes biotherapies. Lastly, unlike adults, cardiac function normalized rapidly within a few days. However, coronary artery wall ultrasound brightness and sometimes dilation of its proximal part, as seen in KD, were noticed, justifying long-term follow-up.

Children are indeed less susceptible to SARS-CoV-2

Several explanations have been proposed to account for the apparent paradox between the frequent viral respiratory diseases observed in children all year round, but particularly during winter, e.g. human rhinoviruses (Groups A, B and C, > 100 serotypes), respiratory syncytial viruses (A & B), influenza viruses (A & B, several subtypes), parainfluenza viruses (type 3 being most common), human metapneumoviruses (subgroups A & B), adenoviruses (> 50 serotypes), enteroviruses (echo & coxsackie) and common coronaviruses (OC43, 229E, NL63 and HKU1) [6], and the new SARS-CoV-2. One explanation lies in the fact that SARS-CoV-2 infects epithelial respiratory cells through angiotensin converting enzyme-2 receptors, which are less numerous and mature in children than in adults [7].

The extent to which children and adolescents are infected by and transmit SARS-CoV-2 is unclear. The role of children and adolescents in the transmission of SARS-CoV-2 depends on susceptibility, symptoms, viral load, social contact patterns and behaviour. To systematically review the susceptibility to and transmission of SARS-CoV-2 among children and adolescents compared with adults, a total of 13,926 studies were identified through PubMed or medRxiv up to 28 July 2020 [8]. A total of 32 studies comprising 41,640 children and adolescents and 168,945 adults met the inclusion criteria, including 18 contact-tracing studies and 14 population-screening studies. The pooled odds ratio of being an infected contact in children compared with adults was 0.56 [95% confidence interval (CI) 0.37–0.95], with substantial heterogeneity ($I^2 = 94.6\%$). Three school-based contact-tracing studies found minimal transmission from child cases, although seroprevalence in adolescents appeared similar to adults. The recent diffusion of SARS-CoV-2 new variants in the community, such as B.1.1.7, which is more contagious, did not result in an appreciably different clinical course to the original strain in children and young people [9].

MIS-C

Mid-April 2020, the South Thames Retrieval Service, London, referred eight children with shock associated with elevated cardiac biomarkers (i.e. troponin and B-type natriuretic peptide) and inflammatory markers (e.g. C-reactive

protein, ferritin and D-dimers) over just 10 days, compared with the usual 1–2 monthly cases of KD [10]. Remarkable were both the clinical features (e.g. high fever lasting > 4 days, diarrhoea, cutaneous rash and conjunctivitis), similar to KD, and the unusually low diastolic pressure as seen in toxic shock syndrome (TSS), caused by TSS toxin 1 released by methicillin-resistant *Staphylococcus aureus* or Group A *Streptococcus* [4]. Six of these children were of Afro-Caribbean descent, and four were obese (body mass index > 25 kg/m²). Although there was no primary respiratory failure, most children were intubated and mechanically ventilated because of shock. Most required vasopressors (e.g. norepinephrine and/or milrinone), and one ultimately required extracorporeal membrane oxygenation (ECMO) support. All children tested negative for SARS-CoV-2 in either nasopharyngeal swabs or bronchoalveolar lavage, but four had known parental exposure. All children were given IGIVs (2 g/kg) within the first 24 hours and antibiotic coverage, including ceftriaxone and clindamycin. Subsequently, six children were given oral aspirin (50 mg/kg/day). A common echocardiographic finding was echo-bright coronary vessels, which progressed to giant coronary aneurysms in one patient, 1 week after hospital discharge. All the children, except the one on ECMO who died from a brain haemorrhage, were actually discharged from the paediatric intensive care unit (PICU) after 4 to 6 days.

In France, 35 children with shock associated with severe left ventricular dysfunction and marked inflammatory syndrome were identified retrospectively in 14 French PICUs over 2 months [11]. The median age at admission was 10 years (range 2–16 years). Co-morbidities were present in 28%, including asthma and being overweight. Gastrointestinal symptoms were predominant at the early stage, associated with clinical signs suggestive of KD, i.e. skin rash, conjunctivitis and red and cracked lips. Left ventricular ejection fraction was < 30% in one third of the cases; 80% required inotropic support and 28% went on ECMO. Inflammatory markers were suggestive of cytokine storm [median interleukin (IL)-6 135 pg/mL; interquartile range (IQR) 87–115 pg/mL] and macrophage activation (D-dimers 5284 ng/mL; IQR 4069–9095 ng/mL). B-type natriuretic peptide was markedly elevated (5743 pg/mL; IQR 2648–11,909 pg/mL), as was high-sensitivity troponin (347 ng/L; IQR 186–1267 ng/L). Thirty-one of 35 patients (88%) tested positive for SARS-CoV-2 infection by polymerase chain reaction (PCR) of nasopharyngeal swabs or serology. All patients received IGIV, and one third received adjunctive steroid therapy. No patient died, and all patients supported by ECMO were successfully weaned off. The median time to full recovery was rather short (2 days; IQR 2–5 days), as found in another case series of acute myocarditis and MIS-C where the patients recovered fully without the need for ECMO [12].

A time-series analysis at Robert Debré Hospital in the Paris area, a French epicentre of the coronavirus disease 2019 (COVID-19) first wave outbreak, recorded the number of hospital admissions to the Paediatric Emergency Department for KD over the past 15 years [13]. Between 01 Dec 2005 and 20 May 2020, 230 patients were diagnosed as having KD, which was estimated by the quasi-Poisson model as 1.2 per month (IQR 1.1–1.3). In April 2020, a rapid increase of KD related to SARS-CoV-2 was identified [six cases per

Table 1 Clinical and laboratory features of multisystem inflammatory syndrome in children [16], Kawasaki disease [15], Kawasaki disease shock syndrome [15] and toxic shock syndrome [4].

	MIS-C	KD	KDSS	TSS
Age	> 8 years	< 5 years		Any age
Fever	> 5 days	> 5 days		> 39 °C
Suggestive signs	At least one among: exanthem; conjunctival hyperhaemia; cracked lips; cervical adenopathy	At least four among: exanthem; conjunctival injection; cracked lips; cervical adenopathy; peeling extremities	At least four among: exanthem; conjunctival injection; cracked lips; cervical adenopathy; peeling extremities	At least one among: diffuse erythroderma; desquamation of extremities; conjunctival hyperhaemia
Cardiac dysfunction	Acute myocarditis; hypoTA (diastolic)	Acute myocarditis	Acute myocarditis; shock	HypoTA (diastolic)
Coronary dilation	10%	10%	10%	None
Gastrointestinal	Diarrhoea; vomiting	Diarrhoea; vomiting	Diarrhoea; vomiting	Diarrhoea; vomiting
Musculoskeletal		Myalgias; arthralgias		Severe myalgias
Inflammatory markers	Elevated CRP; lymphopenia; elevated D-dimers; hypoalbuminaemia	Elevated CRP; leukocytosis; thrombocytosis; hypoalbuminaemia		Elevated CRP; leukocytosis or leukopenia; thrombocytopenia
Cardiac biomarkers	Elevated BNP, troponin			
Aetiology	SARS-CoV-2 PCR or serology	So far none	So far none	Blood cultures: Group A <i>Streptococcus</i> or <i>Staphylococcus aureus</i> (TSS-1)
Treatment	Inotropes + fluids; IVIGs + steroids	Antiplatelets; IVIGs ± steroids	Inotropes; IVIGs ± steroids	Inotropes + fluids; IV antibiotics (ceftriax- one + clindamycin)

BNP: B-type natriuretic peptide; CRP: C-reactive protein; hypoTA: hypotension; IV: intravenous; IVIG: intravenous immunoglobulin; KD: Kawasaki disease; KDSS: Kawasaki disease shock syndrome; MIS-C: multisystem inflammatory syndrome in children; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TSS: toxic shock syndrome; TSS-1: toxic shock syndrome toxin-1.

month; 497% increase (95% CI 72–1082); $P=0.0011$), starting 2 weeks after the peak of the pandemic. SARS-CoV-2 was actually the only virus circulating during the period, and was found in eight of 10 patients (80%) with KD, with positive PCR or serology. A second peak of hospital admissions as a result of KD was also observed in December 2009 [six cases per month; 365% increase (95% CI 31–719); $P=0.0053$], concomitant with the influenza A H1N1 pandemic.

Fifty-eight children [median age 9 years; IQR 5.7–14.0 years; 33 (57%) girls; 40 (60%) of African or Asian descent] from eight hospitals in England were admitted between 23 March and 16 May 2020 with persistent fever and laboratory evidence of inflammation, meeting the published definition of PIMS-TS [14]. All children presented with persistent fever for 3 to 19 days and a variable combination of vomiting [26/58 (45%)], abdominal pain [31/58 (53%)] and diarrhoea [30/58 (52%)]. Rash was present in 30 of 58 (52%) cases, and conjunctival injection in 26 of 58 (45%) cases. Laboratory evaluation was consistent with marked inflammation, with median C-reactive protein 229 mg/L (IQR 156–338 mg/L) and ferritin 610 µg/L (IQR 359–1280 µg/L). Of the 58 children, 29 developed shock that required inotropic support

and fluid resuscitation, including 23/29 (79%) who received mechanical ventilation. Thirteen children met the American Heart Association definition of KD [15]; 23 had fever and inflammation without features of shock and KD. Comparison of PIMS-TS ($n=58$) with other cohorts of KD ($n=1132$), KD shock syndrome (KDSS) ($n=45$) and TSS ($n=37$) showed differences in clinical and laboratory features that suggest that this new disorder differs from other paediatric inflammatory entities (Table 1). PIMS-TS generally occurred in children older than those with KD and KDSS, and with different laboratory features (Fig. 1).

Similar cases, this time quoted as MIS-C, were described in 53 paediatric health centres across the USA [16]. Case definition included six criteria: age < 21 years, fever that lasted for at least 24 hours, laboratory evidence of inflammation, evidence of infection with SARS-CoV-2 based on reverse transcription PCR, antibody testing or exposure to persons with COVID-19 in the past month, multisystem organ involvement and serious illness leading to hospitalization (Table 1). From 15 March to 20 May 2020, 186 children with MIS-C were identified: 115 (62%) patients were male; 135 (73%) were previously healthy; and 131 (70%) were positive for

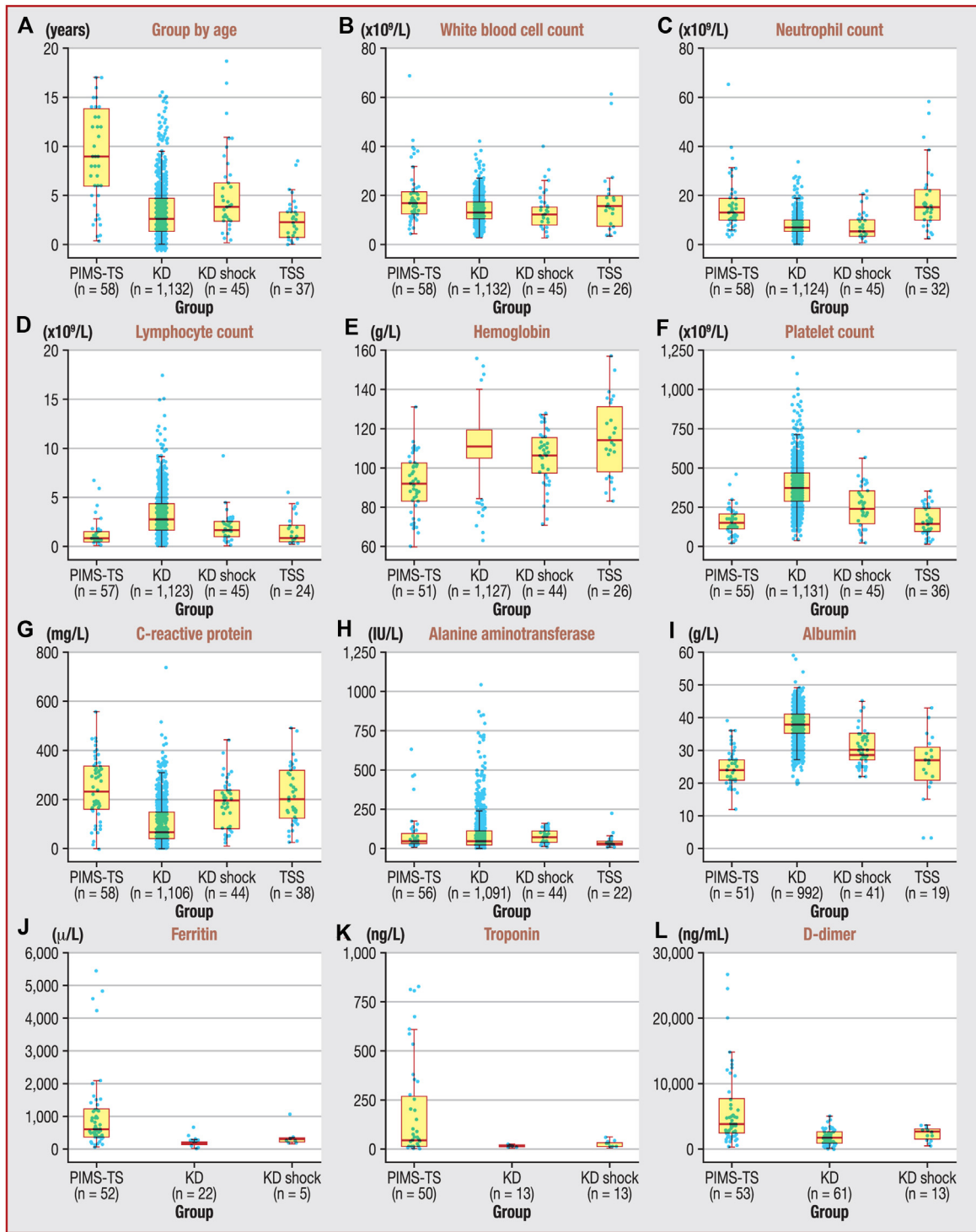


Figure 1. Comparison of age and laboratory results between paediatric inflammatory multisystem syndrome-temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS; $n = 58$), Kawasaki disease (KD; $n = 1132$), KD shock syndrome (KD shock; $n = 45$) and toxic shock syndrome (TSS; $n = 37$) [14] (reproduced with permission). The horizontal lines in the boxes indicate medians; the lower and upper edges of the boxes indicate interquartile ranges and the bars extend to the highest and lowest value within 1.5 times the interquartile range.

SARS-CoV-2 by reverse transcription PCR or antibody testing. Most patients had elevations in at least four markers of inflammation. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), haematological in 142 (76%), mucocutaneous in

137 (74%) and respiratory in 131 (70%). The median duration of hospitalization was 7 days (IQR 4–10 days); 148 (80%) patients were admitted to the PICU, 37 (20%) were mechanically ventilated, 90 (48%) received vasoactive support and four (2%) died. KD-like features were documented

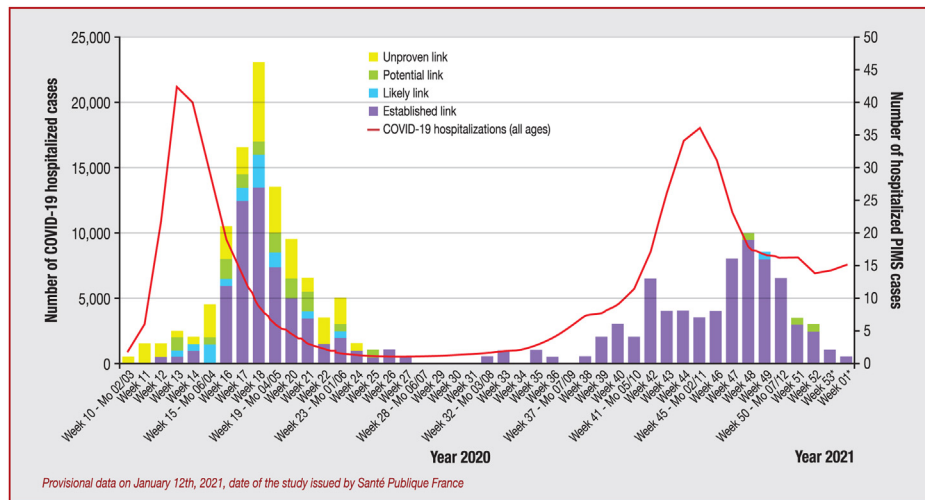


Figure 2. Temporal distribution of hospitalizations for coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C) in France [18].

in 74 (40%) patients, and coronary artery aneurysms (z scores ≥ 2.5) in 15 (8%). The use of immunomodulating therapies was common: IVIG in 144 (77%), glucocorticoids in 91 (49%) and IL-6 or IL-1Ra inhibitors in 38 (20%). Remarkably, MIS-C peaked about 1 month after the nadir of the first wave of the pandemic in the USA.

To address the burden of MIS-C in France, a nationwide prospective surveillance of children hospitalized with SARS-CoV-2 infection was supported by “Santé Publique France” and the French Paediatric Society [17]. Likewise, a sharp increase in the incidence of MIS-C cases occurred about 3 to 4 weeks after the first and second waves of the SARS-CoV-2 pandemic in France (Fig. 2) [18]. Taking advantage of this national database that included 181 children with suspected MIS-C, treatment with IVIG and methylprednisolone versus IVIG alone was associated with a lower risk of treatment failure (odds ratio 0.25, 95% CI 0.09–0.70; $P=0.008$) and a lower risk of use of second-line therapy (odds ratio 0.21, 95% CI 0.06–0.61; $P=0.004$), haemodynamic support, acute left ventricular dysfunction and median duration of stay in the PICU (4 vs. 6 days) [19].

MIS-C and KD: Similar or different pathophysiologies?

The epidemiology, putative pathophysiology, clinical and biological features and current treatment protocols for MIS-C associated with SARS-CoV-2 have been reviewed recently [20]. Key messages are as follows: (1) although SARS-CoV-2 infections in children are generally mild and non-fatal, there is a growing recognition of a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, which can lead to serious illness and long-term side-effects; (2) clinical and laboratory features of MIS-C (Fig. 3) are similar to those of KD, KDSS and TSS, but this syndrome has distinct features and needs a clear clinical and pathophysiological definition; (3) MIS-C might be distinct from KD,

with features including age at onset >7 years, a higher proportion of African or Hispanic children affected and diffuse cardiovascular involvement, suggestive of a generalized immune-mediated disease; (4) the pathophysiology of MIS-C is still unclear, and possible mechanisms include antibody or T-cell recognition of self-antigen (viral mimicry of the host), resulting in autoantibodies, antibody or T-cell recognition of viral antigens expressed on infected cells, formation of immune complexes that activate inflammation and viral superantigen sequences that activate host immune cells; (5) most cases of MIS-C associated with COVID-19 were managed using the standard protocols for KD, with inotropic and vasoactive agents often required in patients with cardiac dysfunction and hypotension, and with anticoagulation also used frequently (clinical research is required to prove the effectiveness and safety of these treatments); and (6) the medium- to long-term outcomes of MIS-C, such as the sequelae of coronary artery aneurysm formation, remain unknown, and close follow-up is important [21].

For almost half a century, the aetiology of KD has remained elusive. Interestingly, a prospective population survey was carried out in the UK and Ireland from 2013 to 2015 [22]. Five hundred and fifty-three cases were notified: 389 had complete KD, 46 had atypical KD and 116 had incomplete KD. Presentation was highest in January and in rural areas. Most children were white (64%), but Chinese and Japanese Asians were over-represented, as were black African or African mixed-race children. Many of these features are also seen in studies from other countries, including the majority of cases being <5 years of age, seasonal occurrence (with more cases in winter and spring), a higher proportion of cases living in rural areas relative to the population distribution and increased proportions of Asians and Africans, suggesting a genetic background. Recently, Rowley et al. isolated peripheral blood plasmablasts from children with KD 1–3 weeks after onset, and prepared 60 monoclonal antibodies [23]. Thirty-two monoclonal antibodies from nine of 11 patients recognized antigens within intracytoplasmic inclusion bodies in ciliated epithelial cells of fatal cases. Five of these monoclonal antibodies, from three patients

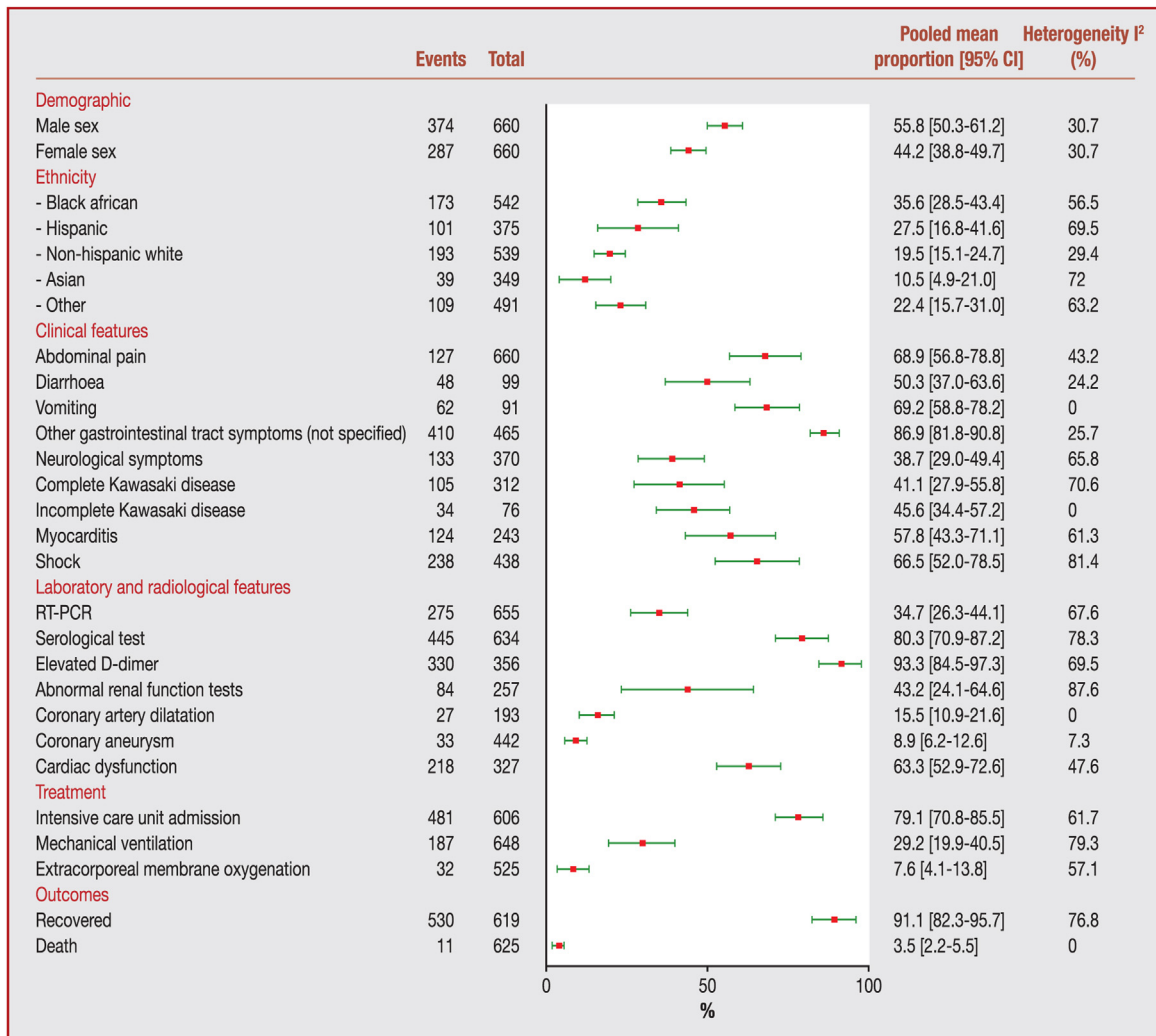


Figure 3. Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 [20] (reproduced with permission). CI: confidence interval; RT-PCR: reverse transcription polymerase chain reaction.

with coronary artery aneurysms, recognized a specific peptide that blocks binding to inclusion bodies. Sera from five of eight patients with KD, day ≥ 8 after illness onset, compared with none of seven infant controls ($P < 0.01$) recognized the KD peptide antigen. Whether the protein epitope derives from a previously unidentified virus remains to be determined. However, monoclonal antibodies recognized related peptides of hepatitis C NS4A using protein phase array. Thus, many lines of evidence now support a ubiquitous viral agent as the cause of KD in genetically susceptible children.

The immunology of MIS-C with COVID-19 has been recently assessed by analyses of blood immune cells, cytokines and autoantibodies in healthy children, children with KD disease enrolled before COVID-19, children infected with SARS-CoV-2 and children presenting with MIS-C [24]. The inflammatory response in MIS-C differs from the cytokine storm of severe acute SARS-CoV-2, shares several features with KD, but also differs from this condition with respect to T-cell subsets, IL-17A and biomarkers associated with arterial damage. Finally, autoantibody profiling suggests multiple autoantibodies, and identified endoglin—a

glycoprotein expressed by endothelial cells and necessary for structural integrity of arteries—as possibly being involved in the pathogenesis of MIS-C.

Conclusions

Although children are generally less susceptible to SARS-CoV-2, and are less sick with very low mortality, a few may develop shock with cardiac dysfunction and diastolic hypotension that requires vasoactive agents and fluid resuscitation. The 2- to 4-week gap between the initial COVID-19 viral phase and the hyperinflammatory phase leads to speculation about the complex interplay between the host immune response, viral antigens and autoimmunity, and similarities or dissimilarities between MIS-C and KD. However, both entities share common therapeutic approaches, including IVIGs and/or corticosteroids, with sometimes a requirement for biotherapies. Nevertheless, the medium- and long-term outcomes of this new disease, particularly

regarding coronary artery aneurysms, remain unknown, and close follow-up is important until adult age.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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