

Multisystem inflammatory syndrome in children: A unique manifestation of COVID-19

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During the coronavirus disease 2019 (COVID-19) pandemic, children have been relatively spared from the severe symptomatic infection affecting adults, particularly the elderly and those with comorbidities. One of the most challenging aspects of paediatric SARS-CoV-2 infection has been the discovery of a unique late manifestation of infection characterised by fever, systemic inflammation and multiorgan involvement. First described in April 2020, it was termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C). Since then, confronting this new childhood inflammatory disorder has been fraught with challenges including variable case definitions, non-specific symptoms, treatment strategies extrapolated from other inflammatory conditions and adult experience, and unknown pathophysiology, risk factors and incidence of severe outcomes or long-term sequelae. Furthermore, although similarities between MIS-C and the well-described Kawasaki disease (KD) suggest that the 2 disorders lie on the same clinical and pathophysiological spectrum, MIS-C has emerged as a distinct entity affecting older children with more intense inflammation, increased shock and gastrointestinal manifestations, more thrombocytopaenia and lymphopaenia, and a greater propensity for myocardial rather than coronary artery injury.

Nadua et al.¹ describe 12 cases of MIS-C in late 2021 after the Delta wave in Singapore, presenting at median age of 7.5 years, at a median interval of 25 days after SARS-CoV-2 infection or exposure. Eleven cases had mild or asymptomatic COVID-19. All developed conjunctivitis and coagulopathy. Half had shock requiring intensive care, while 4 patients required inotropic support. Similar to other studies, gastrointestinal symptoms were commonly seen (75%), followed by neurological (42%), respiratory (33%) and renal (33%) involvement. Fever defervesced quickly at about

2 days and C-reactive protein normalised around 2 weeks, after treatment with intravenous immunoglobulin (IVIg), steroids and aspirin. A range of low- to high-dose steroids was used depending on symptom severity. One child with refractory symptoms improved quickly after receiving anakinra. Overall, there was a short median hospitalisation and intensive care stay of 6 and 3 days, respectively. All patients described survived, while other large studies reported low mortality $\leq 2\%$.^{2,3}

This small case series provides insight into the key demographic Singapore population at risk for MIS-C. Large surveillance studies in Sweden² and the US⁴ have identified young school-aged children to be at the highest risk. Other associated factors are males, foreign-born parents, asthma, obesity and chronic medical conditions. While KD is more common in Japan and East Asia, MIS-C is over-represented in non-Hispanic Black children, who also have a 1.7 odds ratio of decreased cardiac function.⁵ Scarce incidence and outcome data are available for ethnic disparities in East Asia and could not be assessed here, but patients belonged to all 3 main ethnic groups in Singapore. The clinical spectrum seen in Singapore is consistent with previous literature.³ Notably, shock was seen in 50% of MIS-C, significantly more than $<10\%$ of KD. Abrams et al. described such patients as having a sepsis-like presentation with more abdominal pain, shortness of breath, and markedly deranged inflammatory and cardiac biomarkers.⁵

Nadua et al. reported that 83% of their patients had cardiovascular involvement; 8 of 11 children had abnormal echocardiogram findings during admission, and 8 of 10 had elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Cardiac involvement included coronary artery abnormalities (CAAs) in 3 patients from as early as day 4–5 of illness, ventricular dilatation in 3 patients, and reduced cardiac function in 4 patients. Seven of 8 patients with abnormal echocardiograms had complete resolution

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by 6 months post-discharge; reduced cardiac function resolved more quickly than CAAs (median time 14 days versus 42 days, respectively). However, similar to KD, late cardiac sequelae can occur. The authors report 2 Chinese boys, 11 and 4 years old, who had both rash and conjunctivitis. The first had mildly elevated NT-proBNP and a normal echocardiogram on day 7 of illness, but subsequently developed mild coronary artery dilatation on day 50, which was still present on day 218. The other had markedly elevated NT-proBNP and mildly reduced left ventricular function on day 7 resolving by day 10, but later developed mild coronary artery dilatation on day 22 that resolved by day 52. Males and patients with conjunctivitis and mucocutaneous lesions are more likely to develop CAAs, which may reflect a clinical picture more similar to KD.⁵ Elevated proBNP and interleukin-6 are similarly associated with higher risk of CAAs but this threshold is unclear as mildly elevated BNP also occurs in non-cardiac inflammatory conditions.

Significant cardiac sequelae such as heart failure, CAAs and arrhythmias causing long-term morbidity are a major concern for patients and physicians. These may not be immediately apparent, and may occur in children who were not critically ill. So far, limited knowledge suggests a good prognosis. Inflammatory manifestations tend to resolve within 1–4 weeks. Farooqi et al. reported that in 45 children with MIS-C, 1 had persistent mild biventricular dysfunction and 1 had mild mitral and tricuspid regurgitation at 4–9 months.⁶ Davies et al. reported 6 of 68 children had ongoing aneurysms at 86–336 days post-admission.⁷ Although American College of Rheumatology guidelines⁸ recommend echocardiograms at 1–2 weeks, 4–6 weeks, and then 1 year later for those with cardiac involvement during acute MIS-C, and more often for those with ventricular dysfunction or CAAs, it is unclear whether those with no acute cardiac involvement should have a similar follow-up. Arrhythmias presenting only post-acute illness may warrant electrocardiogram surveillance. Despite the rapid resolution of ventricular dysfunction, the occurrence of myocardial fibrosis and scarring as seen in other types of myocarditis may only be detected on cardiac magnetic resonance (CMR) imaging 2–6 months later. However, in a prospective study of 11 children with symptomatic COVID-19 and 6 with MIS-C, of whom 2 MIS-C participants had mild to moderate left ventricle dysfunction and 2 had mild coronary dilation, no significant cardiac disease by CMR and serum cardiac biomarkers were found 1–3

months later.⁹ Larger studies are needed to determine the incidence of long-term myocardial injury, and to guide recommendations on the use of CMR, especially in resource-limited settings.

Diagnosis of MIS-C hinges on the presence of acute SARS-CoV-2 infection in the 2–8 weeks prior to presentation. Changing SARS-CoV-2 testing practices, vaccination, and serologic interpretation make establishing the timing of infection more complicated as the pandemic progresses. In the endemic phase of the pandemic, how recurrent infection affects the risk of developing MIS-C is currently unknown. While COVID-19 is not uncommon, the relative rarity of MIS-C means that investigation of other causes for febrile illness should be thorough to avoid misclassification of conditions with overlapping symptoms like KD shock syndrome, haemophagocytic lymphohistiocytosis, dengue fever, or toxic shock syndrome. International guidelines^{8,10} based on consensus processes outline treatment strategies using immunomodulation, adjunctive antibiotics and/or antivirals, and anti-thrombotic therapy that are broadly similar, with uncertainty over optimal dose and timing of steroid administration, thrombotic and/or bleeding risks, and the benefit of IVIg in myocarditis. Ongoing clinical trials such as the MISTIC and RECOVERY trials will hopefully shed further light. Milder phenotypes with fever, rash, systemic inflammation but less organ involvement may not fulfil current diagnostic criteria, and may be managed conservatively. However, the risk of cardiac sequelae in this setting is unknown and the benefit of empiric IVIg to prevent CAAs is uncertain.

Overall, it is reassuring that MIS-C has a low incidence and mostly favourable outcomes with early diagnosis, aggressive supportive care, and immunomodulation when needed. Reducing the risk of MIS-C could be seen as another reason to prioritise young school-aged children for vaccination. The similarities and differences with KD may contribute to a better understanding of the genetic predispositions and immune mechanisms of the hyperinflammatory host response, even as the pathogenesis of KD has remained elusive for over 50 years. There remain many unknowns; population-based studies in different countries and communities are needed to contribute to evolving our understanding of MIS-C, and to define the pathophysiology, risk factors, and therapeutics to prevent and treat severe outcomes of shock and cardiac sequelae in affected children.

REFERENCES

1. Nadua KD, Chong CY, Kam KQ et al. Multisystem inflammatory syndrome in children in Singapore. *Ann Acad Med Singap* 2022;51:669-96.
2. Rhedin S, Lundholm C, Horne A, et al. Risk factors for multisystem inflammatory syndrome in children – A population-based cohort study of over 2 million children. *Lancet Reg Health Eur* 2022; 19:100443.
3. Jiang L, Tang K, Irfan O, et al. Epidemiology, Clinical Features, and Outcomes of Multisystem Inflammatory Syndrome in Children (MIS-C) and Adolescents—a Live Systematic Review and Meta-analysis. *Curr Pediatr Rep* 2022;10:19-30.
4. Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open* 2021;4:e2116420.
5. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health* 2021;5:323-31.
6. Farooqi KM, Chan A, Weller RJ, et al. Longitudinal Outcomes for Multisystem Inflammatory Syndrome in Children. *Pediatrics* 2021;148:e2021051155.
7. Davies P, du Pré P, Lillie J, et al. One-Year Outcomes of Critical Care Patients Post-COVID-19 Multisystem Inflammatory Syndrome in Children. *JAMA Pediatr* 2021;175:1281-3.
8. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. *Arthritis Rheumatol* 2022;74:e1-20.
9. Webster G, Patel AB, Carr MR, et al. Cardiovascular magnetic resonance imaging in children after recovery from symptomatic COVID-19 or MIS-C: a prospective study. *J Cardiovasc Magn Reson* 2021;23:86.
10. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health* 2021;5:133-41.