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MIS-C: myths have been debunked, but mysteries remain

Jane C. Burns

Although elegant work has detailed the clinical presentation, immune response and disease outcome of multisystem inflammatory syndrome in children, many questions remain. Studies in 2022 have explored the nature of the vascular injury, the role of the SARS-CoV-2 spike protein and the association with the current variants of the virus.

The emergence of multisystem inflammatory syndrome in children (MIS-C) established a new paradigm in infectious disease whereby viral infection resulted in an acute, hyperinflammatory syndrome weeks later. After almost 3 years and >1,000 published reports, however, many features of the pathogenesis of MIS-C remain a mystery. Three topics explored in 2022 include the effect of MIS-C on the coronary arterial wall, the relevance of the SARS-CoV-2 spike protein in MIS-C pathogenesis and the ability of Omicron variants of SARS-CoV-2 to trigger MIS-C.

Controversy persists regarding the impact of MIS-C on the coronary arterial wall and the differences from Kawasaki disease, which remains the most common cause of acquired heart disease in children, with regard to the effects on the coronary artery wall. Clinical details of MIS-C early in the COVID-19 pandemic suggested vascular pathology, including dilated coronary arteries on echocardiography, and laboratory findings of low platelet counts and elevated levels of D-dimer suggested low-grade intravascular coagulation. Medium-term outcomes, however, suggested no persistence of coronary artery damage[1]. In 2022, a pilot study by Fabi et al.[2] documented levels of circulating endothelial cells (CECs) in nine children with Kawasaki disease compared with 20 children with MIS-C, during both acute and subacute phases. The study used a standardized, automated system for assessing CECs (Menarini Silicon Biosystems, Bologna, Italy) that quantifies $CD146^+$ cells in the circulation with appropriate positive and negative cell-surface markers for CECs. Of interest, in the subacute phase numbers of CECs were higher in Kawasaki disease (45.8 cells per ml, interquartile range (IQR) 18.5–131.0) than in MIS-C (3.6 cells per ml, IQR 1.8–21.6; $P = 0.01$), which suggests ongoing endothelial damage in Kawasaki disease but not MIS-C (Fig. 1). Human endothelial cells of cardiac origin express the SARS-CoV-2 receptor ACE2 but do not support viral replication, which could explain the relative sparing of the coronary artery endothelium in MIS-C[3]. Although infiltration of the coronary arterial wall by neutrophils and monocytes followed by T lymphocytes has been well-documented in Kawasaki disease, no similar data are available for MIS-C. In the USA, thousands of MIS-C cases and more than 70 deaths have been reported to date. Yet despite these deaths in US children, no comprehensive autopsy reports describe the histologic characteristics of the coronary arteries in fatal MIS-C cases. Only a few autopsy cases have been published from other countries, and these reports lack details of the vascular pathology. Thus, while there remains a knowledge gap regarding coronary artery pathology in MIS-C, the weight of the current evidence suggests only transient dilation of the coronary arteries with minimal disruption of the endothelium and vascular wall.

Another topic of controversy is the role of the SARS-CoV-2 spike protein in MIS-C. Superantigens are proteins that can activate a large repertoire of T cells by cross-linking class II HLA and either the α or β chain of the T cell receptor (TCR) variable domain, thus bypassing the usual antigen-specificity of the T cell response. Early in the COVID-19 pandemic, computer modelling suggested a sequence in the SARS-CoV-2 spike protein that had characteristics of a potential superantigen that could bind the TCRVβ chain[4]. Subsequently, several groups documented skewing of the TCR repertoire in children with MIS-C with increased expression of the *TRBV11-2* gene, which encodes TCRVβ21.3 (ref. 5). However, in 2022 Amormino et al.[6] found no intrinsic superantigen-like activity of the SARS-CoV-2 spike by comparing the production of pro-inflammatory cytokines in the $TCRV\beta3^+$ Jurkat T cell line and in human $CD4^+$ and $CD8^+$ T cells stimulated with either SARS-CoV-2 spike or staphylococcal enterotoxin B, a well-studied superantigen. In support of this observation, Franco et al.[7] (a group in which I was included) studied the T cell response to pools of SARS-CoV-2 peptides in children in the subacute phase of MIS-C. Although Vβ21.3-bearing $CD4^+$ and $CD8^+$ T cells were numerous, they were not within the SARS-CoV-2-specific T cell population. This finding suggested that in the majority of children this T cell repertoire expanded in response to a non-SARS-CoV-2 related antigen. The triggering antigen is unknown but could potentially enter from the leaky gut, which is known to be

Key advances

- Although coronary artery dilation is associated with both multisystem inflammatory syndrome in children (MIS-C) and Kawaski disease, there is currently no evidence of long-term coronary artery damage in MIS-C[2].
- The SARS-CoV-2 spike protein does not seem to act as a superantigen that binds the Vβ-chain of the T cell receptor[6]; the skewing of Vβ21.3 expression on T cells in children with MIS-C is most likely attributable to a non-SARS-CoV-2 related antigen[7].
- The incidence and severity of MIS-C declined during the Omicron wave of the COVID-19 pandemic as compared with earlier waves, although the precise reason for this decline remains to be determined[10].

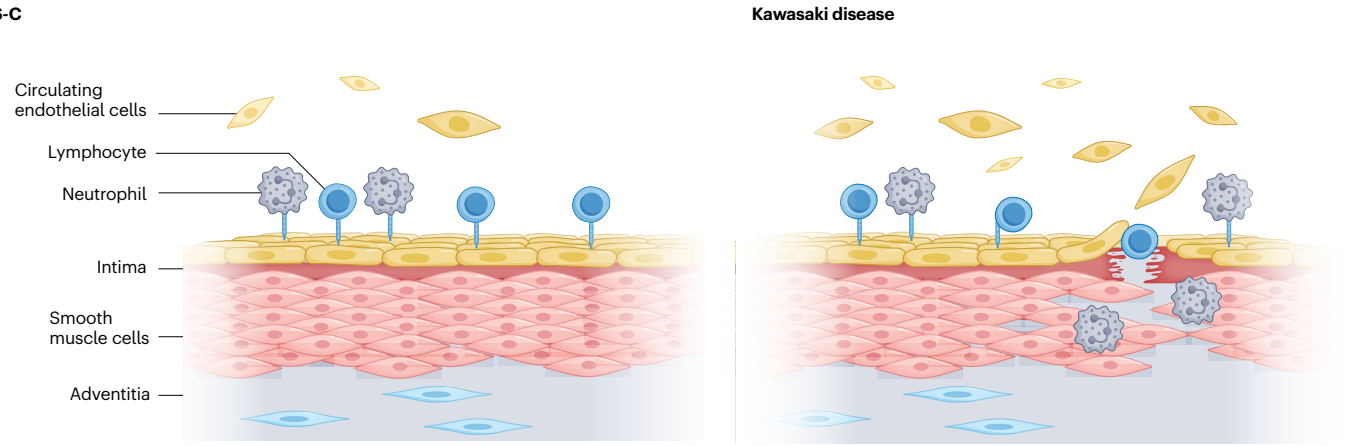

Fig. 1 | Contrasting vascular injury in MIS-C and Kawasaki disease. In multisystem inflammatory syndrome in children (MIS-C), approximately one-quarter of patients had minimal circulating endothelial cells, with highest numbers in the acute, inflammatory phase of the disease. By contrast, in Kawasaki disease, shedding of endothelial cells occurred in the majority of patients and increased from the acute to the subacute phase, suggesting ongoing damage to the architecture of the vascular wall[2].

inflamed in MIS-C[8]. These same children still had numerous Vβ21.3$^+$ CD4$^+$ and CD8$^+$ T cells in circulation 6–14 months after full recovery from MIS-C, thus making it unlikely that these T cells are related to the acute pathogenesis of MIS-C.

If spike peptides are not superantigens, then what is the role of the spike protein in MIS-C pathogenesis? Several groups reported the persistence of the spike antigen in the circulation of patients with acute MIS-C. However, Sigal et al.[9] used a sensitive electrochemiluminescent immunoassay in a multicentre cohort of patients with MIS-C and showed no persistence of spike antigen in the plasma. Thus, these results do not support the hypothesis that circulating spike protein in patients with MIS-C is involved in disease pathogenesis.

In the past year, reports from different countries have documented a decrease in the prevalence of MIS-C in association with Omicron variant waves of SARS-CoV-2 infection, which again raises the question of the role of the spike protein in MIS-C pathogenesis. Levy et al.[10] reported the results of a prospective study in 12 Israeli hospitals over a 16-week period during each of three pandemic waves (Alpha, Delta and Omicron) and found less-severe cardiac outcomes during the Omicron wave with reduced admission to intensive care. Nationwide data for MIS-C incidences in Israel per 100,000 persons younger than 18 years were 54.5 during Alpha, 49.2 during Delta and 3.8 during Omicron. Possible explanations for the decreased incidence of MIS-C during the Omicron wave include mutations in the spike protein leading to reduced pathogenesis, a protective role of previous infection with SARS-COV-2 or vaccination.

Whatever the reason, the worldwide decrease in MIS-C cases is welcome, but this decrease might preclude studies of MIS-C pathogenesis that have sufficient power to support robust conclusions and therefore impede a complete understanding of disease pathogenesis. Nonetheless, research in 2022 has addressed some of the more puzzling aspects of MIS-C pathogenesis and has managed to put several myths to rest.

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Competing interests

The author declares no competing interests.