Children are relatively spared by the SARS-CoV-2 infection or developed a milder disease compared to adults. However, between April and May 2020, several reports described an acute multisystem hyperinflammatory condition, whose signs and symptoms resembled in part those of Kawasaki disease (KD). This condition was also marked by typical clinical manifestations (less common in KD), such as gastrointestinal complaints and myocarditis, often leading to myocardial failure and shock. In addition, patients’ age is older than that of children with classic KD. Management is based on administering intravenous immunoglobulin, glucocorticoids, and anakinra in the most severe instances. It is still debated whether MIS-C and KD are different illnesses or represent a disease continuum.

Abstract
One of the most challenging and intriguing phenomena observed during the COVID-19 pandemic has been the multisystem inflammatory syndrome in children (MIS-C). Patients with this condition present with some clinical features similar to those of Kawasaki disease (KD) and display signs and symptoms that are uncommon or rarely occur in this disorder, such as gastrointestinal complaints and myocarditis, often leading to myocardial failure and shock. In addition, patients’ age is older than that of children with classic KD. Management is based on administering intravenous immunoglobulin, glucocorticoids, and anakinra in the most severe instances. It is still debated whether MIS-C and KD are different illnesses or represent a disease continuum.

KEYWORDS
children, COVID-19, Kawasaki disease, macrophage activation syndrome, multisystem inflammatory syndrome, SARS-CoV-2, toxic shock syndrome

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During all waves of the COVID-19 pandemic, many children with an inflammatory disorder meeting the American Heart Association (AHA) criteria for classic or incomplete KD were seen in affected countries. Many of these cases appeared to be related to SARS-CoV-2 infection, as they tested positive on either RT-PCR or serology. It is, thus, plausible that at least a portion of the cases of 'genuine' KD observed during the pandemic was linked to SARS-CoV-2, analogous to MIS-C. Furthermore, of the 149 cases recorded in Italy between February and May 2020, 96 met the AHA criteria for KD, 10 met the same criteria plus the case definition for MIS-C, and another 43 only met the case definition for MIS-C. This distribution, as well as the occurrence of the two diseases in the same population, during the same period, and when Italian children were exposed to virtually no infectious agent other than SARS-CoV-2 due to lockdown confinement, suggests that the cases observed constitute a disease continuum, with KD and MIS-C at the more benign and severe end of the spectrum, respectively.

The published series have shown that many children with MIS-C who did not fulfill the AHA criteria for KD had persistent fever and that a variable proportion displayed one or more of the typical clinical manifestations of KD (rash, conjunctivitis, lips or oral changes, erythema/edema of the extremities, or cervical lymphadenopathy). One of the arguments favoring the diversity of the two illnesses is that children with MIS-C have a high frequency of signs and symptoms that are unusual or rarely occur in KD, especially gastrointestinal complaints, myocardial injury, and signs of meningeal irritation. However, all these features can be seen in the classic KD. The development of coronary artery dilatation or aneurysms in some patients with MIS-C is another major similitude between the two conditions.

Compared with KD, MIS-C is marked by more intense inflammation and the frank tendency toward the development of shock. However, toxic shock syndrome (TSS), which is seen in around 5% of children with KD, has many aspects in common with the shock syndrome of MIS-C. Thrombocytopenia is another feature of MIS-C that is not typical of KD, which is characterized by thrombocytosis. However, a drop in platelet count is frequently encountered in TSS. A further distinctive hematologic abnormality of MIS-C is lymphopenia, which may directly affect the viral infection.

There are several similarities in the therapeutic approach to MIS-C and KD. A high proportion (70–80%) of children with MIS-C have been treated initially with IVIG, which is part of the standard protocol for KD. In case of nonresponse to IVIG, shock, or organ-threatening disease, adjunctive therapy with glucocorticoids was usually given, analogous to the regimens proposed for IVIG-refractory KD. The IL-1 inhibitor anakinra has been occasionally employed for the treatment of MIS-C refractory to IVIG and glucocorticoids. This biologic agent is also proposed for the management of KD. A further similarity between the two conditions is the self-limited clinical course, which usually lasts 2–3 weeks.

A feature that is emphasized as distinguishing MIS-C from KD is that the median age of MIS-C (9–10 years) is higher than that of KD (< 5 years). Several reasons may explain why MIS-C spares young children. Firstly, young children have an immune system more active against viral infections for the repeated vaccinations. Moreover, they show a cross-protection induced by MMR vaccine, which shares some antigenic determinants with SARS-CoV-2, a cross-reactive immunity elicited after the previous encounter with other coronaviruses involved in community respiratory tract infections, a lower expression of the ACE2 enzyme, and a lesser ability of the immature immune system to mount a hyperinflammatory response.

The etiology of KD is unknown, but it is generally considered the consequence of an abnormal immune response, in genetically predisposed children, to infectious triggers entering through the upper respiratory tract. Multiple infectious agents have been suspected over the years, including the respiratory RNA virus. In the case of MIS-C, an extremely aggressive and invasive virus like SARS-CoV-2, which has shown the capacity to cause a cytokine storm syndrome in the lung of adults with COVID-19, could induce, in case of a massive viral load, a clinical phenotype much more inflammatory and acute than that of KD, and marked, in addition to the typical manifestations of KD, by a higher frequency of less typical or atypical disease manifestations and serious complications, especially myocarditis and TSS. The development of a KD or a MIS-C phenotype after contact with SARS-CoV-2 might depend on several factors, including virulence of viral strains, child age, intensity or kinetics of the immune response, ethnic or socioeconomic factors, comorbidities (particularly obesity), and genetic background. Recently, rare inborn errors of immunity altering the immune response to SARS-CoV-2 have been highlighted as possible pathogenetic factors of MIS-C in some children.

In conclusion, we favor the hypothesis that MIS-C is on the KD spectrum instead of representing a new disorder separate from KD. The occurrence of a KD-like condition in association with SARS-CoV-2 infection underscores that KD is not a disease, but a syndrome, whose main phenotype and severity depend on the magnitude and type of the immune response and the characteristics of the host and triggering agent. Further studies of the genetic and immunopathologic background are required to establish the relationship between MIS-C and KD. Notably, the pathology that has emerged during the pandemic will pave the way for investigations aimed to shed light on the etiology of MIS-C.
on the etiopathogenesis of KD and of other inflammatory disorders whose causative factors and mechanisms are still elusive.

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CONFLICT OF INTERESTS
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Maria Santaniello: Writing—original draft (equal). Caterina Matucci-Cerinic: Writing—review and editing (equal). Valentina Natoli: Writing—review and editing (equal). Chiara Trincianti: Writing—review and editing (equal). Francesca Ridella: Writing—review and editing (equal). Angelo Ravelli: Conceptualization (equal); Supervision (lead); Writing—review and editing (equal).

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