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Editorial: COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C)

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Abstract

In early 2020, at the beginning of the coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rare cases were reported in children and adolescents of multisystem inflammatory syndrome in children (MIS-C). MIS-C is characterized by fever, systemic inflammation, and multiorgan dysfunction and usually presents late in SARS-CoV-2 infection. Since May 2020, the Centers for Disease Control and Prevention (CDC) has recorded all reported cases of COVID-19 and MIS-C in children and adolescents in the USA. In April 2021, the American College of Rheumatology (ACR) revised its clinical guidelines for diagnosing and managing hyperinflammation and MIS-C. There are several challenges ahead for preventing, diagnosing, and managing MIS-C, particularly following the rapid emergence of new strains of SARS-CoV-2. This Editorial aims to present an update on the current status of the clinical presentation, diagnosis, and management of MIS-C and includes some updates from population studies and clinical guidelines.

Keywords:

Editorial • Pediatric Multisystem Inflammatory Disease, COVID-19 Related • Severe Acute Respiratory Syndrome Coronavirus 2

In early 2020, at the beginning of the coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cases of COVID-19 were reported in children and adolescents. Rare cases of multisystem inflammatory syndrome in children (MIS-C) were initially reported in England and the USA [1,2]. Cases of MIS-C were initially described as Kawasaki-like or toxic shock-like syndromes [3,4]. Although adults and children experience single organ or multiorgan inflammation during the acute infectious phase of SARS-CoV-2, usually as COVID-19 pneumonia, by mid-2020, MIS-C was identified as a specific condition [5].

Throughout 2020, case reports and case series from several countries identified a spectrum of disease severity and clinical course in children and adolescents with COVID-19 that had similarities and differences from adult forms of COVID-19 [6,7]. Since May 2020, the US Centers for Disease Control and Prevention (CDC) has recorded all reported cases of MIS-C in children and adolescents who have been diagnosed with COVID-19 [8]. The CDC criteria for a diagnosis of MIS-C include age <21 years with a clinical presentation of fever, clinically severe illness requiring hospitalization, laboratory evidence of inflammation, multisystem organ involvement, and positive laboratory testing for current or recent SARS-CoV-2 infection, or SARS-CoV-2 exposure within four weeks before the onset of symptoms [8]. According to the CDC, as of April 1, 2021, there were 3,000 reported cases of MIS-C in the USA, with a median age of 9 years (range, 5-15 years), and 60% were male [8].

A positive test result for SARS CoV-2 was found in 99%, but the remaining 1% of children were in contact with someone with COVID-19 [8].

In April 2021, the American College of Rheumatology (ACR) revised its clinical guidelines for diagnosing and managing hyperinflammation and MIS-C associated with pediatric cases of SARS-CoV-2 infection [9]. The latest ACR guidance continues to be updated as more cases are diagnosed and as the understanding of the pathogenesis and management of MIS-C evolves [9]. There is now clinical consensus that there are two rare and distinct severe conditions in children infected with SARS-CoV-2 [9]. Hyperinflammation, or the effects of 'cytokine storm' during the acute phase of SARS-CoV-2 infection, is now distinguished from MIS-C, which is a late manifestation of SARS-CoV-2 infection in children, characterized by fever, systemic inflammation, and multiorgan dysfunction [9]. The ACR has also provided clinical recommendations for children with hyperinflammation during the acute infectious phase of SARS-CoV-2 infection [9].

Although clinical diagnostic and management guidelines are being developed, the diagnosis of MIS-C remains challenging because children can present with non-specific symptoms, including fever, respiratory tract infection, loss of taste and smell [8,9]. Severe MIS-C can present with clinical features similar to toxic shock syndrome, myocarditis, meningitis, sepsis, or systemic vasculitis [8,9]. However, children who have been in

contact with adults with COVID-19 and who present with fever, conjunctivitis, rash, and abdominal symptoms should undergo rapid testing for SARS-CoV-2 infection and should be referred to a specialist pediatric infectious diseases unit [8,9].

There are several challenges ahead for preventing, diagnosing, and managing MIS-C, particularly with the rapid emergence of new strains of SARS-CoV-2 [10]. In May 2021, the findings were published from one of the largest cohorts of patients with MIS-C, including 1,080 children admitted to US hospitals between May 14 and October 19, 2020 [11]. The findings showed that identifying key demographic and clinical characteristics could lead to earlier diagnosis and management and prevent severe outcomes for patients with MIS-C [11]. Data from this study showed that admission to pediatric intensive care units (PICUs) and impaired cardiac function, shock, and myocarditis were more common in children between 6-12 years and 13-20 years when compared with children aged 0-5 years [11]. Impaired cardiac function, shock, and myocarditis were more common in children requiring admission to the PICU [11]. Also, increased serum levels of C-reactive protein (CRP), ferritin, troponin, D-dimer, brain natriuretic peptide (BNP), and interleukin-6 (IL-6), or reduced platelet or lymphocyte counts were associated with disease severity [11]. Coronary artery abnormalities were more common in male children and children with mucocutaneous lesions or conjunctivitis [11].

Although guidelines are now developing for the diagnosis and supportive care of patients with MIS-C, the results of clinical trials on safety and efficacy for treatments are still awaited [10].

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Conclusions

MIS-C is a rare acute association with SARS-CoV-2 infection in children. International clinical diagnostic and management guidelines have been developed for MIS-C and are continually updated. The diagnosis of MIS-C is challenging because children can present with non-specific symptoms. Severe MIS-C can present with clinical features similar to toxic shock syndrome, myocarditis, meningitis, sepsis, or systemic vasculitis. However, children who have been in contact with adults with COVID-19 and who present with fever, conjunctivitis, rash, and systemic symptoms should undergo rapid testing for SARS-CoV-2 infection and should be referred to a specialist pediatric infectious diseases unit.