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, 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.
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].

Patients with MIS-C are managed supportively and treated with intravenous immunoglobulin (IVIG), methylprednisolone, and biologics, but the results of therapeutic clinical trials are awaited [8-10]. Clinical trials involving very ill children are difficult to conduct. One of the main ongoing trials is the UK RECOVERY trial (NCT04381936), supported by the Bill and Melinda Gates Foundation. The RECOVERY trial is due for completion in December 2021 and is one of the few trials randomly assigning patients with MIS-C to the biologics, tocilizumab or anakinra. A further challenge is identifying children who may be most at risk from developing MIS-C at the time of presentation with SARS-CoV-2 infection and those with severe disease requiring admission to the PICU [10].

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.

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