EDITORIAL

Epidemiology of Multisystem Inflammatory Syndrome in Children
A Step Closer to Understanding Who, Where, and When

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Death and disease in adult patients from the COVID-19 pandemic continue unabated across the world well into 2021,[1] and why children have escaped severe disease from this virus[2] remains one of the most intriguing gaps in our understanding of the immune response to this virus. Of equal imperative, what insights can be gained via a deeper understanding as to why some children do become critically ill from COVID-19 and the more recently described multisystem inflammatory syndrome in children (MIS-C)? Unlocking the key immunologic mechanisms driving these outcomes will likely initially emerge from meticulous epidemiologic studies that describe the few children who do get very ill from this disease.

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In this issue of *JAMA Pediatrics*, a study by Belay et al[3] is a notable step forward in answering these questions by providing greater insight into the epidemiology of MIS-C. This cross-sectional study of children with MIS-C, including a total of 1733 cases across the United States, is the largest study to date describing the clinical findings and temporal trends.[3] The design of such a study is not without challenges. Notably, children with severe COVID-19 and MIS-C do not infrequently have overlapping symptoms. As the objective of this study was exclusively the epidemiology of MIS-C, the investigators specifically excluded from enrollment any child with exclusively respiratory symptoms, respiratory symptoms and rash with SARS-CoV-2 polymerase chain reaction positivity, or negative serological testing for SARS-CoV-2. While this study design was intended to enhance the precision of the definition of MIS-C, compelling research has reported overlap of some characteristics between children with COVID-19 and MIS-C, most notably positive SARS-CoV-2 serology in both cohorts.[4] It must also be noted that neither the US Centers for Disease Control and Prevention nor the World Health Organization MIS-C definitions require positive SARS-CoV-2 serology; they both only require evidence of prior infection, which would include contact with a known SARS-CoV-2–positive individual.[5,6] As affirmation of these study design concerns, a study recently published in *JAMA* found that respiratory disease alone was not found to be a distinguishing characteristic between severe acute COVID-19 and MIS-C.[7]

The study by Belay and colleagues[3] advances our understanding of the presentation of MIS-C in 3 important ways. First, it provides more precision on the range of presenting symptoms and outcomes, including cardiovascular disease. In particular, practitioners and researchers alike now have greater insight on the presentation of MIS-C symptoms by age. As reported here, Belay et al[3] found that younger children present more frequently with conjunctival findings, rash, and abdominal pain, while adolescents present more frequently with chest pain, shortness of breath, and cough. In this study, cardiac dysfunction and a diagnosis of myocarditis was significantly more likely in adolescents. Most notably, this study of MIS-C found no significant difference in the age of children with coronary artery dilation. Coronary artery dilation was found in 18.3% of children aged 0 to 4 years and 14.6% of children aged 18 to 20 years.

Second, this study defines characteristics of MIS-C by preceding symptomatology of COVID-19. In the younger patient group, 16% to 18% of patients had preceding symptoms of COVID-19, and in the older group, between 44% and 63% reported preceding symptoms consistent with acute COVID-19. This follows trends of asymptomatic COVID-19 in younger patients but adds that the MIS-C incidence per 100 000 in the group of 0- to 4-year-old patients was 2.3 while in the group of 18- to 20-year-old patients was only 0.4. Pediatric clinicians should note that children who have not shown any evidence of having had COVID-19 are at higher risk for MIS-C, despite being relatively infrequent on a population scale. However, health care professionals can be reassured by the findings that younger patients had fewer cardiovascular complications and admissions to the intensive care unit. Further delineation was offered comparing patients who had prior symptomatic COVID-19 vs those who did not in Table 2.[3]

Third, the accumulating literature provides further validation of the prevailing hypothesis that MIS-C is a postinfectious mediated disorder, given the temporal and geographic distribution of MIS-C with COVID-19 reported here. Additionally, by study protocol, the date of July 1, 2020, was chosen to define early MIS-C cases vs later MIS-C cases. Belay et al[3] found that children diagnosed with MIS-C before July 1, 2020, had significantly more cardiac dysfunction, myocarditis, and more elevated pro–brain natriuretic peptide with decreased lymphocyte values. Whether these findings are associated with temporal changes in the virus, reflect ascertainment bias to a new and widely reported syndrome, or both will require further investigation.

Going forward, the pediatric community now has a more refined understanding of the presentation of the subtle differences between a child presenting with COVID-19 or MIS-C. Most prominently in differentiating between these 2 disease processes, the lack of prior COVID-19 symptoms, especially in the younger age group, should not reassure pediatric practitioners that this child is risk free of potential cardiac manifestations from MIS-C. If the entirety of the world's pediatric population is at risk for

COVID-19 and vaccination will be delayed in the pediatric population compared with adults, this potentially severe outcome must remain at the forefront of the differential diagnosis for pediatricians across the world pending further outcome research. While it is reassuring that recently published research indicates that those with MIS-C and cardiac dysfunction improve over the near term,[7] the long-term effects on ventricular dysfunction in these children remain unknown and thus is now a major focus of research.

Essential gaps in our understanding of MIS-C and the overall effect of COVID-19 on children remain. Given the imprecision of the case definition, more sensitive and specific diagnostic tests are needed to distinguish children with MIS-C from COVID-19 more accurately. Moreover, further research is needed to assess the most effective and efficient therapies to treat serious and life-threatening presentations and long-term sequalae of MIS-C. Long-term follow-up investigations of children with MIS-C and COVID-19 are underway and essential, as the one constant in this pandemic has been the unanticipated challenges it has presented. Last, while most children across the world have been spared from the life-threatening ravages of this disease, it is equally true that they have been exposed to unprecedented challenges to their well-being and future. As investigators determine new risks associated with long-term SARS-CoV-2, medicine will stand increasingly prepared to meet the challenges ahead.

ARTICLE INFORMATION

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