INVITED COMMENTARY

Pediatric COVID-19 and MIS-C – Lessons Learnt and the Way Forward

S BALASUBRAMANIAN,[1*] AISHWARYA VENKATARAMAN,[2] AV RAMANAN[3]

[1]KanchiKamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu, India.

[2]ICMR-National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India.

[3]Bristol Royal Hospital for Children; and Translational Health Sciences, University of Bristol; Bristol, United Kingdom.

*sbsped@gmail.com

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread worldwide leading to innumerable deaths [1,2]. Children are just as likely as adults to get infected and the most common source of infection in children is through close contact [3]. Epidemiology of pediatric COVID-19 has been variable in the literature but overall children account only for approximately 10% of patients diagnosed with COVID-19 infection [3].Of these, approximately one-third were estimated to have occurred in South Asia (including India). Most children are; however, asymptomatic or have mild symptoms [4]. Severe disease may be seen in infants or children who have other comorbidities or underlying conditions [4,5]. There is a knowledge gap concerning this low sensitivity to COVID-19 in children and its mild presentation in the pediatric population. Many hypotheses have been put forward ranging from the possibility of children having an immune response to the virus lesser than the adults to viral interference in the respiratory tract of young children, leading to a lower SARS-CoV-2 viral load [4]. The different expression of the angiotensin converting enzyme 2 receptor (the receptor for SARS-CoV-2) in the respiratory tracts of children and adults has also been attributed to the less severe disease in children [4]. The other possibilities include pre-existing cross-reactive antibody, a protective off-target effect of live vaccines, developmental differences in adaptive immune responses in children, and age-related differences in the nasopharyngeal microbiome.

Fever, cough, nausea, vomiting, diarrhea, skin rashes, fatigue, headaches, and nasal congestion are the common clinical features [5]. Whilst primary infection with SARS-CoV-2 has been relatively benign in children, a small proportion develop multisystem inflammatory syndrome in children (MIS-C) [6].

MIS-C shares the clinical and laboratory features with Kawasaki disease (KD) as both diseases are characterized by systemic inflammation and vascular injury, possibly leading to coronary artery lesions [6]. Therefore as in KD, prompt recognition in MIS-C is important to halt the inflammation and organ damage, especially cardiac failure, hypotension and/or shock. Cardiovascular abnormalities (e.g., heart failure, arrhythmias, myocarditis, pericarditis, cardiogenic shock, pulmonary embolism, ST elevation myocardial infarction, coronary artery aneurysms) have been reported in various case reposts and series [7]. In this issue of this journal, Tomar, et al. [7] have reported various cardiovascular findings in children with MIS-C that included coronary vasculopathy, pericardial effusion, valvular regurgitation, ventricular dysfunction, diastolic flow reversal in aorta, pulmonary hypertension, bradycardia and intracardiac thrombus. They also report a survival rate of 99%, which is in contrast to the 11.7% mortality reported by Poovalhagi, et al. [8] from another tertiary care pediatric center in India,which is also one of the research papers in this issue. However, Poovalhagi, et al. [8] reported acute kidney injury, HLH, need for ventilation and mitral regurgitation as the significant risk factors for mortality in their cohort of children with MIS-C and no mortality was encountered among children without Kawasaki or shock phenotype. The differences in mortality in two different centers in India due to MIS-C might have been due to the differences in the demographic profile and time frame of the study periods.

Neurologic manifestations have been described in children hospitalized with acute COVID-19 and includes febrile and non-febrile seizures, stroke, central nervous system infection/demyelination, Guillain-Barré syndrome/ variants, acute fulminant cerebral edema, headache, weakness, anosmia, ageusia, and delirium. Seizures in febrile children with COVID-19 appear to be more common with the Omicron variant than with earlier variants [9]. Neurological symptoms in children with MIS-C are elaborately described by Herini, et al. [10]

from Indonesia, where the authors report 24% of children with MIS-C having acute neurologic symptoms, thus suggesting the need to consider MIS-C as a diagnostic possibility in any child with acute neurological presentation and fever in this post pandemic era.

There is currently no standardized treatment regimen for MIS-C and supportive treatment is the mainstay. The management of MIS-C is very similar to KD. Various treatment strategies have been used by different centers, but mostly the treatment includes intravenous immunoglobulins, various immune modulators, steroids, aspirin, and anticoagulant therapies [6]. Although previous studies have shown that children with MIS-C receiving both IVIG and steroids had better course than IVIG alone, the clinical evidence of benefit is yet to be established. In a recently published study, Welzel, et al. [11] concluded that recovery rates, including occurrence and resolution of coronary artery aneurysms, were similar for primary treatment with intravenous immunoglobulin when compared to glucocorticoids or intravenous immunoglobulin plus glucocorticoids. Therefore, initial treatment with glucocorticoids appears to be a safe alternative to immunoglobulin or combined therapy, and might be advantageous in view of the cost and limited availability of intravenous immunoglobulin in many countries [12].

India has been significantly impacted by the COVID-19 epidemic, and children are not exempt from its impacts. Around 80 million COVID-19 cases have been reported in India as of March, 2023. Although, adults have been the majority of the cases, children have also been affected [13]. However, it is not possible to determine the extent of infection among children, due to lack of available data. The risk of COVID-19 in children is influenced by a number of factors, including population density, poverty, and access to healthcare [13,14]. Children living in crowded urban areas or in poverty may have been at higher risk of contracting the virus due to difficulties in social distancing and access to proper hygiene facilities. Many asymptomatic children were unlikely to be tested and therefore may not have been reported. Furthermore, co-infection with other microorganisms, such as virus, bacteria and fungi, act as significant challenge in diagnosis, treatment and prognosis of COVID-19 children in tropical country like India. Likewise, the epidemiology of MIS-C in India is still not fully understood, as the condition is relatively rare and cases may be underreported due to limited testing and healthcare access in some areas. Nevertheless, the incidence and severity of MIS-C has declined during the Omicron wave of the COVID-19 pandemic as compared with earlier waves; although, the precise reason for this remains obscure. However, there has been a sudden surge in cases of hand foot mouth disease in both children and adults, as reported by Mohta et al. [15] during the ongoing COVID-19 pandemic. Similar reports have emerged from others places in India during the last three months that describe a sudden surge of H3N2 and adenoviral infections; although, the relationship between COVID-19 and these viral infections is unclear and not clearly understood [16].

There is still uncertainty regarding the future course of COVID-19 and MIS-C in children, and much will rely on how the pandemic develops over time. There have been advancements in both vaccine and therapy, but there are still numerous questions about the long-term consequences of the virus and how it affects children [14].The availability and efficacy of COVID vaccines in children as well as the ongoing clinical trials exploring the safety and efficacy of additional vaccine candidates may influence COVID-19 and MIS-C in this population, with a possibility that these conditions will be reduced. Vaccines have been shown to be effective in reducing the risk of illness, hospitalization, and death from COVID-19 in children. However, the virus' ability to evolve into new forms may be a cause for concern. Even while the present vaccines are effective against the current variants, it is likely that other variants that are more contagious or severe may emerge, which may put children at higher risk of developing COVID-19 and MIS-C, necessitating the development of new prevention and treatment methods. Research on the causes and remedies of MIS-C may also be ongoing. Even while the illness is still not fully understood, future research could provide additional details on its underlying mechanisms and point to potential treatments.

In conclusion, there are important lessons learned from pediatric COVID-19, which include the pattern of infections; importance of timely and accurate diagnosis; the need for more pediatric-specific research into the epidemiology, diagnosis and treatment, and understanding the longterm effects of COVID-19 and MIS-C in children. In addition, there is a definite need for good clinical trials for appropriate use of steroids in viral infections such as dengue, based on the proven benefits of steroids in severe COVID and MIS-C.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020;20:773.
2. Hiscott J, Alexandridi M, Muscolini M, et al. The global impact of the coronavirus pandemic. Cytokine Growth Factor Rev. 2020;53:1-9.
3. Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are

children less susceptible to COVID-19? J Microbiol Immunol Infect.2020;53:371.
4. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr.2020;109:1088-95
5. Venkataraman A, Balasubramanian S, Putilibai S, et al. Correlation of SARS-CoV-2 serology and clinical phenotype amongst hospitalised children in a tertiary children's hospital in India. J Trop Pediatr. 2021;67:fmab015.
6. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334-46.
7. Tomar M, Chaudhuri M, Goel T, et al. Profile of cardiac involvement in children after exposure to COVID-19. Indian Pediatr. 2023 Mar 9: S097475591600505. E-pub ahead of print.
8. Varadarajan P, Elilarasi S, Solomon RS, et al. Multisystem Inflammatory syndrome in children (MIS-C) associated with Covid-19: single-center experience. Indian Pediatr. 2023 mar 9;S097475591600507. E-pub ahead of print.
9. Guimarães D, Pissarra R, Reis Melo A, Guimarães H. Multisystem inflammatory syndrome in children (MISC): a systematic review. Int J Clin Pract. 2021;75:e14450.
10. Herini ES, Iskandar K, Triono A, et al. Neurological manifestations of COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) in Yogyakarta, Indonesia. Indian Pediatr. 2023 Feb 20; S09747559 1600489. E-pub ahead of print.
11. Welzel T, Atkinson A, Schöbi N, et al. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. Lancet Child Adolesc Heal. 2023;7:238-48.
12. Chew C, Ramanan A V. Immunoglobulin, glucocorticoid, or combined therapy for multisystem inflammatory syndrome in children. Lancet Rheumatol. 2023;5:e168-9.
13. Shrestha R, Shrestha L. Coronavirus disease 2019 (Covid-19): A pediatric perspective. J Nepal Med Assoc. 2020;58: 525.
14. Adeyinka A, Bailey K, Pierre L, Kondamudi N. COVID 19 infection: Pediatric perspectives. Journal of American College of Emergency Physicians Open. 2021;2:e12375.
15. Mohta A, Pareek S, Sharma MK, et al. Hand foot mouth disease during SARS-CoV-2 pandemic: a multicentric study. Indian Pediatr. 2023 Mar 9;S097475591600501. E-pub ahead of print.
16. Sapra M, Kirubanandhan S, Kanta P, et al. Respiratory viral infections other than SARS CoV-2 among the North Indian patients presenting with acute respiratory illness during the first COVID-19 wave. VirusDisease. 2022;33:57-64.