

## SARS-CoV-2–Related Inflammatory Multisystem Syndrome in Children Different or Shared Etiology and Pathophysiology as Kawasaki Disease?

Brian W. McCrindle, MD, MPH; Cedric Manlhot, PhD

**The pediatric inflammatory multisystem syndrome (PIMS)** now described in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has generated considerable interest, both for its severity and delayed emergence in an age group largely spared the complications of primary infection, but also for its overlapping clinical features with Kawasaki disease (KD), the leading cause of acquired heart disease in children in high-income countries.<sup>1</sup> This has prompted considerable discussion that the 2 conditions could have different or shared etiologic and pathophysiologic pathways.

The article in this issue of *JAMA* by Whittaker et al<sup>2</sup> carefully described a case series of 58 hospitalized patients with severe presentations of PIMS temporally associated with SARS-CoV-2 (PIMS-TS), and in addition importantly compares the clinical and laboratory features with historical cohorts of patients with KD and with KD shock syndrome. Also in this issue, the Research Letter by Cheung et al<sup>3</sup> described similar clinical characteristics for 17 patients with PIMS, 8 of whom also met criteria for typical KD and 5 for incomplete KD. As illustrated in these reports, the differences between PIMS-TS and KD are just as interesting as the similarities.

Five decades of clues have not elucidated the etiology of KD. A genetic predisposition has already been established, evidenced by a male preponderance, racial predisposition (East Asian individuals), and some increased risk in first-degree relatives of affected individuals and twins.<sup>1,4</sup> This genetic predisposition is partially explained by known susceptibility genes that are associated with the immune system.<sup>5</sup> The epidemiology of KD, with marked variations in incidence between countries,<sup>6</sup> region-specific seasonality,<sup>7</sup> periodic outbreaks, and the existence of spatiotemporal clusters,<sup>8,9</sup> suggests that there is more to the etiology of KD than the genetic component alone. Over the years, associations between the distribution of KD and exposure to infectious agents, pollution levels, local weather conditions, concentration of atmospheric biological particles, and early childhood, habitual, or unfamiliar exposures have been documented and postulated to be implicated in the pathophysiology of KD or even to be the etiologic trigger.<sup>9-12</sup> Conflicting studies have been published for almost all of these associations. Some factors have been shown to apply only at a local level; some are associated with the global distribution of case, but none have been shown to have a direct causal relationship with KD.

One of the most common and consistently reported factors associated with KD are infectious diseases. In addition

to epidemiological associations, the involvement of infectious disease in the etiology of KD is based on the clinical observation that both infectious disease symptoms and culture-proven infections are common in KD, and specific organisms have been described with some clusters of KD. Many infectious organisms have been suggested as the primary etiology, ranging from toxin-producing *Streptococcus* and *Staphylococcus* to *Mycoplasma* species to a large number of viruses, including coronavirus strains NL63 (2006)<sup>13</sup> and 229E (2014),<sup>14</sup> but the associations have been inconsistent or not replicated.<sup>15,16</sup>

Additional clues as to the etiology of KD have come from pathology studies of fatal cases, which have shown the presence of intracytoplasmic inclusion bodies in bronchial epithelium, analyses of which have suggested the possibility of a novel virus.<sup>17</sup> The normal flora may be involved, particularly that of the gastrointestinal tract. Gastrointestinal infections may be involved as either the trigger or altering susceptibility to the trigger. Animal models have used intraperitoneal injection of *Candida albicans* or *Lactobacillus casei* wall extract to induce a KD-like syndrome in mice. Decades of immunologic studies have suggested that KD is associated with a response to a classic antigen, with activation of the innate immune system, but also features of an adaptive immune response.<sup>1</sup> The trigger and the etiologic and pathophysiologic pathways remain complex and elusive.

Based on a series of studies documenting the epidemiological distribution of KD in Canada,<sup>18</sup> including the examination of spatiotemporal clusters,<sup>8</sup> and a case-control environmental epidemiology study,<sup>19</sup> Manlhot et al proposed a comprehensive framework for the time and space distribution of KD. The framework ties together many clues as to the etiology and pathogenesis of the disease and addresses the numerous and apparently disjointed epidemiological associations that have been documented with KD over the years. This framework, which has recently been updated, includes 3 major components: a genetic predisposition to KD, immunomodulation through both habitual exposures and environmental factors, and contact with the disease trigger or triggers. In this framework, exposure to the still unidentified trigger(s) results in the development of KD in a genetically susceptible child, with at least a partial contribution from immune-modulating factors. These factors include those that reduce the risk of KD, such as a more abundant habitual exposure to environmental allergens, and those that increase risk, such as pollution. Multiple factors may act sequentially or simultaneously as predisposing, immune-modulating, or triggering agents, altering both individual risk as well as the

incidence of KD in the population across countries or regions. Potential factors found to be associated with KD, either identified through epidemiological association studies or clinical observations, can be integrated into this framework.

PIMS, which has emerged with the SARS-CoV-2 pandemic, shares multiple clinical and laboratory features with KD, such that a substantial proportion of patients included in early reports of PIMS-TS<sup>20,21</sup> also met the American Heart Association criteria for KD.<sup>1</sup> Whittaker et al<sup>2</sup> reported that 7 of the 58 children met criteria for KD and an additional 6 met criteria if coronary artery aneurysm was included. However, it also is clear that PIMS-TS and KD have substantial differences as well as similarities, as the report by Whittaker et al suggests, with age being a major difference (median age, 9 years for children with PIMS-TS vs 2.7 years for those with KD).<sup>2</sup> These observations lead to some speculation, most importantly, the extent to which the etiology and pathophysiology of KD and PIMS-TS might overlap or share commonalities.

These early observations about the characteristics of patients with MIS have already provided some clues. While both conditions have a similar male preponderance, case series suggest that MIS in children may have a different racial/ethnic predilection, affecting primarily people of African American, Caribbean, and Hispanic ancestry, whereas KD affects primarily those of East Asian ancestry. Does this indicate that PIMS-TS might be mediated by a different set of susceptibility genes, or is this related to other factors that are associated with race/ethnicity, including environment and social factors? PIMS-TS also appears to affect an older age group than KD and has a higher prevalence of gastrointestinal symptoms and lower prevalence of classic KD clinical signs. These differences could be associated with 1 or more factors influencing immunomodulation and susceptibility. These observations suggest some areas where suscep-

tibility and immune-modulating factors for PIMS-TS and KD may contribute differently for each condition.

Another important question is whether SARS-CoV-2 directly triggers MIS in children (or perhaps KD), or is it an intermediate primer or co-stimulatory agent or does coronavirus disease 2019 (COVID-19) provide a portal of entry or exposure for the actual trigger? Both a gastrointestinal and respiratory portal of entry, possibly related to infection, have been proposed for KD, and PIMS-TS has affected both systems. The absence of preceding symptoms of COVID-19, often negative polymerase chain reaction result but sometimes positive antibodies or familial exposure, and development of PIMS-TS after a 3- to 6-week lag suggest that SARS-CoV-2 may be acting either as the trigger or an immune-modulating factor. The response to the SARS-CoV-2 pandemic, such as quarantine and social isolation, may have affected children's level of exposure to environmental factors and infections, providing further immune modulation. There has never been a global outbreak of KD where it might be traced to a specific trigger, but this may now be the case. It might be that this is what a specific, unique, and ubiquitous form of KD looks like, providing an important opportunity for investigations to determine factors associated with variations.

With so many questions, how will clinicians and researchers find answers? Careful determination of the unique features of SARS-CoV-2 and the epidemiology, clinical features, genetic and immunologic susceptibility, and pathophysiologic pathways of both PIMS-TS and KD may help to inform the etiologic and pathophysiologic framework for both conditions. The article by Whittaker et al<sup>2</sup> and Research Letter by Cheung et al<sup>3</sup> mark the beginning of an important time of focused discovery, which will likely have relevance to an entire host of inflammatory conditions.

#### ARTICLE INFORMATION

**Author Affiliations:** Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (McCrindle); Johns Hopkins University School of Medicine, Division of Cardiology, Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland (Manliot).

**Corresponding Author:** Brian W. McCrindle, MD, MPH, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, 555 University Ave, Toronto, ON M5G 1X8, Canada (brian.mccrindle@sickkids.ca).

**Published Online:** June 8, 2020.  
doi:10.1001/jama.2020.10370

**Conflict of Interest Disclosures:** Dr McCrindle reported receiving personal fees from Janssen and serving as an investigator for Janssen and Mezzion. No other disclosures were reported.

#### REFERENCES

1. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing;

Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. doi:10.1161/CIR.0000000000000484

2. Whittaker E, Bamford A, Kenny J, et al; PIMS-TS Study Group; EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. Published online June 8, 2020. doi:10.1001/jama.2020.10369

3. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. Published online June 8, 2020. doi:10.1001/jama.2020.10374

4. Uehara R, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease in parents and children. *Acta Paediatr*. 2003;92(6):694-697. doi:10.1111/j.1651-2227.2003.tb00602.x

5. Onouchi Y, Gunji T, Burns JC, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary

artery aneurysms. *Nat Genet*. 2008;40(1):35-42. doi:10.1038/ng.2007.59

6. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child*. 2015;100(11):1084-1088. doi:10.1136/archdischild-2014-307536

7. Burns JC, Herzog L, Fabri O, et al; Kawasaki Disease Global Climate Consortium. Seasonality of Kawasaki disease: a global perspective. *PLoS One*. 2013;8(9):e74529. doi:10.1371/journal.pone.0074529

8. Hearn J, McCrindle BW, Mueller B, et al. Spatiotemporal clustering of cases of Kawasaki disease and associated coronary artery aneurysms in Canada. *Sci Rep*. 2018;8(1):17682. doi:10.1038/s41598-018-35848-9

9. Nagao Y, Urabe C, Nakamura H, Hatano N. Predicting the characteristics of the aetiological agent for Kawasaki disease from other paediatric infectious diseases in Japan. *Epidemiol Infect*. 2016;144(3):478-492. doi:10.1017/S0950268815001223

10. Awaya A, Sahashi N. The etiology of Kawasaki disease: does intense release of pollen induce pollinosis in constitutionally allergic adults, while constitutionally allergic infants develop Kawasaki disease? *Biomed Pharmacother*. 2004;58(2):136-140. doi:10.1016/j.biopha.2003.08.026

11. Zeft AS, Burns JC, Yeung RS, et al. Kawasaki disease and exposure to fine particulate air pollution. *J Pediatr*. 2016;177:179-183.e1. doi:10.1016/j.jpeds.2016.06.061
12. Fujiwara T, Shobugawa Y, Matsumoto K, Kawachi I. Association of early social environment with the onset of pediatric Kawasaki disease. *Ann Epidemiol*. 2019;29:74-80. doi:10.1016/j.annepidem.2018.10.010
13. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005;191(4):499-502. doi:10.1086/428291
14. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. *J Med Virol*. 2014;86(12):2146-2153. doi:10.1002/jmv.23950
15. Dominguez SR, Anderson MS, Glodé MP, Robinson CC, Holmes KV. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki syndrome. *J Infect Dis*. 2006;194(12):1697-1701. doi:10.1086/509509
16. Lehmann C, Klar R, Lindner J, Lindner P, Wolf H, Gerling S. Kawasaki disease lacks association with human coronavirus NL63 and human bocavirus. *Pediatr Infect Dis J*. 2009;28(6):553-554. doi:10.1097/INF.0b013e31819f41b6
17. Rowley AH, Baker SC, Arrollo D, et al. A protein epitope targeted by the antibody response to Kawasaki disease. *J Infect Dis*. Published online February 13, 2020. doi:10.1093/infdis/jiaa066
18. Manlhiot C, O'Shea S, Bernknopf B, et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. *Can J Cardiol*. 2018;34(3):303-309. doi:10.1016/j.cjca.2017.12.009
19. Manlhiot C, Mueller B, O'Shea S, et al. Environmental epidemiology of Kawasaki disease: linking disease etiology, pathogenesis and global distribution. *PLoS One*. 2018;13(2):e0191087. doi:10.1371/journal.pone.0191087
20. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;(May):13. doi:10.1016/S0140-6736(20)31103-X
21. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1