Kawasaki Disease and Multisystem Inflammatory Syndrome in Children: An Antibody-Induced Mast Cell Activation Hypothesis

Darrell O. Ricke, PhD[1], Nicole Gherlone, BS[2], Philip Fremont-Smith, MS[1] & Philip Tisdall, MD[3]

[1]MIT Lincoln Laboratory
[2]Frank H. Netter MD School of Medicine – Quinnipiac University
[3]Medical School Companion LLC

Multisystem Inflammatory Syndrome in Children (MIS-C, previously designated as Pediatric Multisystem Inflammatory Syndrome - PMIS) is appearing in infants, children, and young adults in association with COVID-19 (coronavirus disease 2019) infections[1,2]. Kawasaki Disease (KD, previously called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood[3]. KD presents with similar symptoms to MIS-C especially in severe forms such as Kawasaki Disease Shock Syndrome (KDSS). The cause of KD is currently unknown; KD has features similar to those associated with viral infection. The leading hypothesis is that a ubiquitous infectious agent can induce KD in a genetically susceptible patient[4]. This hypothesis is supported by the presence of IgA plasma cells identified in inflamed tissues and coronary arteries of KD patients[5]. Associations between KD and multiple pathogens have been reported, including: adenovirus[6,7], human bocavirus[8], coronavirus[7], human coronavirus 229E[9], human coronavirus (HCoV-NH) NL63[10], cytomegalovirus[11], dengue[12,13], enterovirus[7,14], Epstein–Barr virus[15], human herpesvirus 6[16], human lymphotropic virus[17], human rhinovirus[7], influenza[18], measles[19], parvovirus B19[20,21], parainfluenza virus type 2[22], respiratory syncytial virus (RSV)[23], rotavirus[24], varicella zoster (chicken pox)[25,26], torque teno virus[27], Staphylococcus aureus[28], and Streptococcus[15,29]. Postinfluenza vaccination KD has also been reported[30]. The seasonality and temporal clustering of KD[23,31] further support an infectious etiology. A mild cold may precede the onset of KD and up to one third of patients have concurrent, confirmed infections at the time of KD diagnosis[32]. The aggregate of these pathogen associations with KD support the rejection of the hypothesis that KD is caused by a single infectious agent. The alternative hypothesis is that KD is associated with multiple infectious agents. We hypothesize that MIS-C may be atypical KD or a KD-like disease associated with SARS-CoV-2[33] as a result of antibody dependent enhancement activation of mast cells. We further hypothesize that KD and MIS-C may be induced in part by histamine and other inflammatory molecules released from activation of mast cells by Fc receptor bound pathogen antibodies resulting in a hyperinflammatory response.

The diagnosis of classic KD is based on the presence of fever lasting five days or longer together with at least four of five additional clinical findings: bilateral conjunctivitis, oral mucosal changes, cervical lymphadenopathy, extremity changes, and a polymorphous rash. However, not all patients present with this complete clinical picture. Atypical KD occurs in patients with fever lasting five days or longer with two or three of the previously mentioned clinical features. MIS-C symptoms demonstrate remarkable overlap (Table 1) and patients can meet criteria for atypical KD[34]. Accurate diagnosis is also complicated by difficulties distinguishing early KD symptoms from any common skin rash. As KD progresses, complications such as coronary

artery aneurysms, heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusions may develop and lead to significant morbidity and mortality. KDSS is a complication of KD resulting in shock and hypotension. KDSS can present with multi-organ dysfunction and is associated with more severe inflammatory markers and coronary artery abnormalities[35] similar to the clinical presentation of MIS-C. The observed symptoms for MIS-C and KD are consistent with Mast Cell Activation Syndrome (MCAS) characterized by inflammatory molecules released from activated mast cells. Pathogen binding to antibodies already attached to FcεRI and/or FcγRI receptors can activate mast cells, leading to release of histamine and other compounds. Elevated histamine levels can lead to smooth muscle cell contraction in various organs, vasodilation, increased vascular permeability, and increased gastric acid section. This would result in clinical findings such as tachycardia, hypotension, erythema, edema, arrhythmias, urticaria, and diarrhea. Histamine also causes contractions of endothelial and pericyte cells[36] resulting in impeded blood flow through capillaries; this is well characterized for cerebral blow flow following ischemic events[37]. We hypothesize that both COVID-19 patients and MIS-C patients may have the same impeded blood flow through capillaries likely due to increased histamine levels. In some patients, pressure from impeded blood flow within cardiac capillaries may result in increased coronary artery blood pressure leading to aneurysms, a well-known complication in KD (Figure 1). We hypothesize that KD and MIS-C coronary artery aneurysms could be due to increased back pressure from stimulated contracted effector cells within the heart capillaries and not due to inflammatory weakening of the arterial wall.

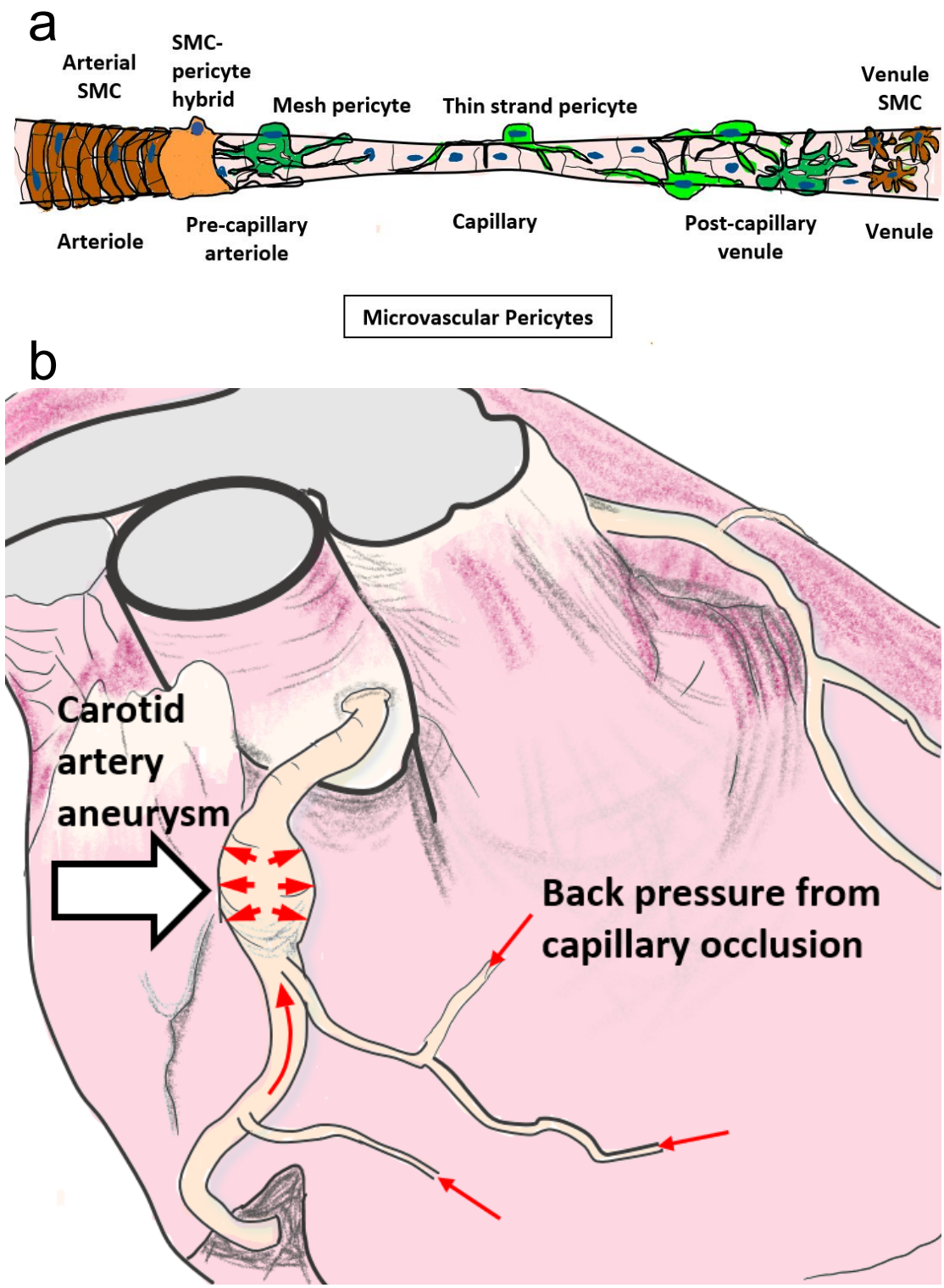
Table 1. Similarities between MSI-C, KD, and KDSS (a subtype of KD)

	KD	KDSS	MIS-C
Demographics	<5 years (80%), (Asian)	3 years (mean), (Asian, Hispanic)	infant[1]-25[38] years (mean)
Symptoms	Fever[a] + 1. cervical lymphadenopathy 2. exanthematous polymorphous rash 3. extremity changes (initial presentation is redness and edema followed in 1-2 weeks by desquamation of hands and feet) 4. bilateral nonsuppurative conjunctivitis 5. oral mucosal changes (strawberry tongue)	Fever[a] + 1. cervical lymphadenopathy 2. exanthematous polymorphous rash 3. extremity changes (desquamation of hands and feet) 4. bilateral nonsuppurative conjunctivitis 5. oral mucosal changes (strawberry tongue) • neurologic alterations • abdominal pain • diarrhea • vomiting • shock	• Prolonged fever • swollen lymph nodes (lymphadenopathy) • rash (variable) • extremity changes (peripheral edema) • red or pink eyes • irritability/sluggishness • abdominal pain • diarrhea • vomiting • shock

Cardiac	Coronary artery abnormalities (dilation, aneurysm)	Coronary aneurysms (66%), valvular involvement, pericardial effusion[35]	Moderate to very severe myocardial involvement, coronary artery aneurysms[c], pericardial effusion, arrhythmia
Labs	Elevated CRP (8.2 mg/dL average)[39], Thrombocytosis Elevated AST/ALT Leukocytosis/neutrophilia Anemia Elevated NT-proBP Elevated troponin (in up to 1/3rd of acute KD)[39] Pyuria	Elevated CRP >7 mg/dL (92%)[35] Albumin <3.5 g/dL Thrombocytosis[c] Elevated AST/ALT Leukocytosis/neutrophilia Anemia Elevated bilirubin	Impressively high CRP >16.9[40] Thrombocytopenia Elevated AST/ALT Neutrophilia Lymphocytopenia Anemia Elevated NT-proBNP Elevated troponin Hypoalbuminemia Elevated D-dimer /ferritin/triglycerides
Treatment	IVIG and aspirin	IVIG[d], corticosteroids, aspirin	IVIG and aspirin

[a]5 consecutive days without identifiable source
[b]MSI-C patients with coronary abnormalities may have had KD and were misclassified
[c]in one study, 54% of patients presented with thrombocytopenia
[d]Higher incidence of IVIG resistance

Figure 1. Model for coronary artery aneurysms and heart failure due to impeded blood flow. (a) Model of microvascular region for pericyte cell occlusion (b) coronary artery aneurysm caused by increased pressure from capillaries with impeded blood flow.



Pediatric patients with first COVID-19 infection generally have less severe clinical manifestations than adult patients[42]. The COVID-19 asymptomatic infection rate has been estimated in adults to be 46%[43] and 46% in children in Hubei, China[44]. The COVID-19 outbreak in New York started mid-March, 2020. Children with MIS-C symptoms similar to KD associated with COVID-19 infections have been reported since late April, 2020[45] suggesting that MIS-C manifests more than one month after the peak of COVID-19 cases in an affected area[46]. The number of affected children is rising rapidly; within weeks of the publication of COVID-19 related MIS-C cases[2], 93 children were diagnosed with up to five deaths in New York. As of May 29th, 186 cases have been identified[47]. With an observed New York population infection rate of roughly 1.7% (337,055 infected[48] of 19,450,000 population), the timing is consistent with a possible second wave of pediatric SARS-CoV-2 infections (1.7% x 1.7% of 1.7 million New York children, or 491 possible second infections in New York children). With a rate of 306 cases per 100,000 under age 18 adjusted to 567 for asymptomatic children, the 1.7% infection rate of 1.7 million New York children predicts 169 possible second infections. The 186 cases identified by May 29th represents between 110% of the lower estimate of 169 infections to 38% of the 491 that would be predicted in a second wave of infections. This second wave hypothesis is consistent with the lack of MIS-C patients in China and elsewhere that contained outbreaks in their regions consequently avoiding or minimizing a second wave of infections. With more than 250 cases of MIS-C reported in the United States by May 21, 2020[49], MIS-C may reflect a subset of children initially infected with SARS-CoV-2 who sustained a subsequent exposure to the virus. MIS-C may be a manifestation of a delayed trigger from antibody-dependent disease. Without an effective vaccine for COVID-19, first exposure to COVID-19 may result in asymptomatic to mild disease for most children accompanied with risk for MIS-C/KD upon subsequent infection. Ricke and Malone[50] predict antibody-dependent enhancement disease risks associated with COVID-19 based on disease enhancements from animal model vaccine studies of severe acute respiratory syndrome, Middle East respiratory syndrome, and other coronaviruses. Extending this hypothesis to these children predicts that this post infectious inflammatory process (MIS-C or KD) could be a direct result of antibody-dependent enhancement (ADE) of disease for children previously infected with SARS-CoV-2 or primary infected infants with either transplancental transferred antibodies (matAbs) or SARS-CoV-2 antibodies from breast milk. Children diagnosed with a post infectious inflammatory process (MIS-C or KD) frequently test negative on PCR for SARS-CoV-2[1], however, they test positive for antibodies of SARS-CoV-2[40,46] suggesting antibodies are required for disease manifestation.

The symptoms of MIS-C and KD are consistent with activation of mast cells via antibodies as seen in Mast Cell Activation Syndromes (MCAS). We hypothesize that SARS-2 antibodies created after first infection bind mast cells, triggering histamine release. These antibodies may be recognizing low levels of SARS-CoV-2 from a re-emergent infection or a possible second exposure. Mast cell released histamine stimulates pericytes or effector cells causing capillary constriction, notably in cardiac tissue. The MIS-C/KD symptoms of diarrhea and vomiting may be attributed to increased histamine levels and/or SARS-CoV-2 gastrointestinal infection akin to symptoms seen for severe acute respiratory syndrome. Current KD and MIS-C treatments includes intravenous gamma globulin (IVIG) which reduce the swelling and inflammation in

blood vessels; IVIG can decrease, but not eliminate, this risk of developing coronary artery aneurysms. We hypothesize that IVIG dilutes the current infection pathogen antibodies bound to mast cells, reducing the level of mast cell activation. This ADE model for MIS-C and COVID-19 emphasizes the importance of developing safe T-cell vaccines and increases the importance for safety testing for any B-cell vaccines being developed. In addition to IVIG, famotidine and other potential treatments have been identified by Malone et al.[51] We suggest children presenting with evidence of MSI-C/KD should also be tested for antibodies for SARS-CoV-2 as PCR testing is frequently negative.

Conclusion

We must be cautious of inappropriately creating new clinical entities in the context of COVID-19[52]. It has been hypothesized before the advent of COVID-19 that KD could be induced by RNA viruses in genetically susceptible hosts. It is also possible we are seeing SARS-CoV-2 induced KD complicated by KDSS in MIS-C as a result of antibody dependent enhancement activation of mast cells.

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References

1 Jones, V. G. *et al.* COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hospital Pediatrics*, hpeds.2020-0123, doi:10.1542/hpeds.2020-0123 (2020).

2 Russo, M. *Up to 5 NY Children Dead, 93 Sickened by Rare COVID-Related Illness*, <https://www.nbcnewyork.com/investigations/kawasaki-disease-up-to-5-ny-children-dead-85-sickened-by-rare-covid-related-illness/2411571/> (2020).

3 Newburger, J. W., Takahashi, M. & Burns, J. C. Kawasaki Disease. *Journal of the American College of Cardiology* **67**, 1738-1749, doi:https://doi.org/10.1016/j.jacc.2015.12.073 (2016).

4 Shulman, S. T. & Rowley, A. H. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nature Reviews Rheumatology* **11**, 475-482, doi:10.1038/nrrheum.2015.54 (2015).

DISTRIBUTION STATEMENT A. Approved for public release. Distribution is unlimited.

5 Soni, P. R., Noval Rivas, M. & Arditi, M. A Comprehensive Update on Kawasaki Disease Vasculitis and Myocarditis. *Current Rheumatology Reports* **22**, 6, doi:10.1007/s11926-020-0882-1 (2020).
6 Embil, J. A., McFarlane, E. S., Murphy, D. M., Krause, V. W. & Stewart, H. B. Adenovirus type 2 isolated from a patient with fatal Kawasaki disease. *Can Med Assoc J* **132**, 1400-1400 (1985).
7 Chang, L.-Y. *et al.* Viral infections associated with Kawasaki disease. *J Formos Med Assoc* **113**, 148-154, doi:10.1016/j.jfma.2013.12.008 (2014).
8 Catalano-Pons, C. *et al.* Detection of human bocavirus in children with Kawasaki disease. *Clinical Microbiology and Infection* **13**, 1220-1222, doi:https://doi.org/10.1111/j.1469-0691.2007.01827.x (2007).
9 Shirato, K. *et al.* Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. *J Med Virol* **86**, 2146-2153, doi:10.1002/jmv.23950 (2014).
10 Esper, F., Weibel, C., Ferguson, D., Landry, M. L. & Kahn, J. S. Evidence of a Novel Human Coronavirus That Is Associated with Respiratory Tract Disease in Infants and Young Children. *J Infect Dis* **191**, 492-498, doi:10.1086/428138 (2005).
11 Catalano-Pons, C. *et al.* Primary Cytomegalovirus Infection, Atypical Kawasaki Disease, and Coronary Aneurysms in 2 Infants. *Clinical Infectious Diseases* **41**, e53-e56, doi:10.1086/432578 (2005).
12 Jagadeesh, A., Krishnamurthy, S. & Mahadevan, S. Kawasaki Disease in a 2-year-old Child with Dengue Fever. *The Indian Journal of Pediatrics* **83**, 602-603, doi:10.1007/s12098-015-1927-8 (2016).
13 Sopontammarak, S., Promphan, W., Roymanee, S. & Phetpisan, S. Positive Serology for Dengue Viral Infection in Pediatric Patients With Kawasaki Disease in Southern Thailand. *Circulation Journal* **72**, 1492-1494, doi:10.1253/circj.CJ-08-0158 (2008).
14 Weng, K.-P. *et al.* Enterovirus Infection and Subsequent Risk of Kawasaki Disease: A Population-based Cohort Study. *The Pediatric Infectious Disease Journal* **37** (2018).
15 Kikuta, H., Nakanishi, M., Ishikawa, N., Konno, M. & Matsumoto, S. Detection of Epstein-Barr virus sequences in patients with Kawasaki disease by means of the polymerase chain reaction. *Intervirology* **33**, 1-5, doi:10.1159/000150224 (1992).
16 Okano, M. *et al.* Human herpesvirus 6 infection and Kawasaki disease. *J Clin Microbiol* **27**, 2379-2380 (1989).
17 Okano, M. Kawasaki Disease and Human Lymphotropic Virus Infection. *Current Medical Research and Opinion* **15**, 129-134, doi:10.1185/03007999909113373 (1999).
18 Joshi, A. V., Jones, K. D. J., Buckley, A.-M., Coren, M. E. & Kampmann, B. Kawasaki disease coincident with influenza A H1N1/09 infection. *Pediatrics International* **53**, e1-e2, doi:10.1111/j.1442-200X.2010.03280.x (2011).
19 Whitby, D. *et al.* Isolation of measles virus from child with Kawasaki disease. *The Lancet* **338**, 1215, doi:https://doi.org/10.1016/0140-6736(91)92085-G (1991).
20 Holm, J. M., Hansen, L. K. & Oxhøj, H. Kawasaki disease associated with parvovirus B19 infection. *European Journal of Pediatrics* **154**, 633-634, doi:10.1007/BF02079066 (1995).
21 Nigro, G. *et al.* Active or recent parvovirus B19 infection in children with Kawasaki disease. *The Lancet* **343**, 1260-1261, doi:https://doi.org/10.1016/S0140-6736(94)92154-7 (1994).

22 Keim, D., Keller, E. & Hirsch, M. MUCOCUTANEOUS LYMPH-NODE SYNDROME AND PARAINFLUENZA 2 VIRUS INFECTION. *The Lancet* **310**, 303, doi:https://doi.org/10.1016/S0140-6736(77)90990-4 (1977).
23 Kim, G. B. *et al.* Evaluation of the Temporal Association between Kawasaki Disease and Viral Infections in South Korea. *Korean Circ J* **44**, 250-254, doi:10.4070/kcj.2014.44.4.250 (2014).
24 Matsuno, S., Utagawa, E. & Sugiura, A. Association of Rotavirus Infection with Kawasaki Syndrome. *J Infect Dis* **148**, 177-177, doi:10.1093/infdis/148.1.177 (1983).
25 Ogboli, M. I., Parslew, R., Verbov, J. & Smyth, R. Kawasaki disease associated with varicella: a rare association. *British Journal of Dermatology* **141**, 1136-1152, doi:10.1046/j.1365-2133.1999.03231.x (1999).
26 Kossiva, L., Papadopoulos, M., Lagona, E., Papadopoulos, G. & Athanassaki, C. Myocardial infarction in a 35-day-old infant with incomplete Kawasaki disease and chicken pox. *Cardiology in the Young* **20**, 567-570, doi:10.1017/S1047951109991478 (2010).
27 Thissen, J. B. *et al.* A novel variant of torque teno virus 7 identified in patients with Kawasaki disease. *PLoS One* **13**, e0209683-e0209683, doi:10.1371/journal.pone.0209683 (2018).
28 Hall, M., Hoyt, L., Ferrieri, P., Schlievert, P. M. & Jenson, H. B. Kawasaki Syndrome-Like Illness Associated with Infection Caused by Enterotoxin B-Secreting Staphylococcus aureus. *Clinical Infectious Diseases* **29**, 586-589, doi:10.1086/598638 (1999).
29 Shinomiya, N. *et al.* Variant Streptococcus sanguis as an etiological agent of Kawasaki disease. *Prog Clin Biol Res* **250**, 571-572 (1987).
30 Shimada, S., Watanabe, T. & Sato, S. A Patient with Kawasaki Disease Following Influenza Vaccinations. *The Pediatric Infectious Disease Journal* **34** (2015).
31 Burns, J. C. *et al.* Seasonality and temporal clustering of Kawasaki syndrome. *Epidemiology* **16**, 220-225, doi:10.1097/01.ede.0000152901.06689.d4 (2005).
32 Benseler, S. M. *et al.* Infections and Kawasaki Disease: Implications for Coronary Artery Outcome. *Pediatrics* **116**, e760, doi:10.1542/peds.2005-0559 (2005).
33 Verdoni, L. *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*, doi:10.1016/S0140-6736(20)31103-X.
34 Leon, M. P. D. *et al.* COVID-19 Associated Pediatric Multi-System Inflammatory Syndrome. *Journal of the Pediatric Infectious Diseases Society*, doi:10.1093/jpids/piaa061 (2020).
35 Gamez-Gonzalez, L. B. *et al.* Kawasaki disease shock syndrome: Unique and severe subtype of Kawasaki disease. *Pediatrics International* **60**, 781-790, doi:10.1111/ped.13614 (2018).
36 Kelley, C., D'Amore, P., Hechtman, H. B. & Shepro, D. Vasoactive hormones and cAMP affect pericyte contraction and stress fibresin vitro. *Journal of Muscle Research & Cell Motility* **9**, 184-194, doi:10.1007/BF01773740 (1988).
37 Attwell, D., Mishra, A., Hall, C. N., O'Farrell, F. M. & Dalkara, T. What is a pericyte? *J Cereb Blood Flow Metab* **36**, 451-455, doi:10.1177/0271678X15610340 (2016).

38 *MIS-C: Young adults also affected by Kawasaki-like disease*, <https://www.washingtonpost.com/health/2020/05/21/misc-c-kawasaki-coronavirus-young-adults/> (2020).
39 Sato, Y. Z. *et al.* Cardiovascular biomarkers in acute Kawasaki disease. *International Journal of Cardiology* **164**, 58-63, doi:https://doi.org/10.1016/j.ijcard.2011.06.065 (2013).
40 Riphagen, S., Gomez, X., Gonzalez-Martinez, C., Wilkinson, N. & Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. *The Lancet* **395**, 1607-1608, doi:10.1016/S0140-6736(20)31094-1 (2020).
41 *COVID Digital Pathology Repository*, <https://covid19pathology.nih.gov/> (2020).
42 Dong, Y. *et al.* Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics*, e20200702, doi:10.1542/peds.2020-0702 (2020).
43 He, W., Yi, G. Y. & Zhu, Y. Estimation of the basic reproduction number, average incubation time, asymptomatic infection rate, and case fatality rate for COVID-19: Meta-analysis and sensitivity analysis. *medRxiv*, doi:10.1101/2020.04.28.20083758 (2020).
44 Dong, Y. *et al.* Epidemiology of COVID-19 Among Children in China. *Pediatrics*, e20200702, doi:10.1542/peds.2020-0702 (2020).
45 *Fact Sheet: Pediatric Multisystem Inflammatory Syndrome*, <https://www1.nyc.gov/assets/doh/downloads/pdf/imm/covid-19-pmis.pdf> (2020).
46 Shulman, S. T. Pediatric COVID-associated Multi-system Inflammatory Syndrome (PMIS). *Journal of the Pediatric Infectious Diseases Society*, doi:10.1093/jpids/piaa062 (2020).
47 *Childhood Inflammatory Disese Related to COVID-19*, <https://coronavirus.health.ny.gov/childhood-inflammatory-disease-related-covid-19> (2020).
48 *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*, <https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6> (2020).
49 Czachor, E. *More Than 250 Cases of Coronavirus-Linked Inflammatory Disease MIS-C Have Been Reported in the U.S.*, <https://www.newsweek.com/more-250-cases-coronavirus-linked-inflammatory-disease-mis-c-have-been-reported-us-1505812> (2020).
50 Ricke, D. O. & Malone, R. W. *Medical Countermeasures Analysis of 2019-nCoV and Vaccine Risks for Antibody-Dependent Enhancement (ADE)* (Preprints, 2020).
51 Malone, R. W. *et al.* COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. *Preprint (Version1) at ResearchSquare*, doi:10.21203/rs.3.rs-30934/v1 (2020).
52 Loomba, R. S., Villarreal, E. & Flores, S. Covid-19 and Kawasaki syndrome: should we really be surprised? *Cardiology in the Young*, 1-5, doi:10.1017/S1047951120001432 (2020).