MIS-C and PIMS:
The Alphabet Soup of COVID-associated Hyperinflammation in Children

By Tala El Tal, MD; and Rae S. M. Yeung, MD, FRCPC, PhD

Patient Case:

An eight-year-old previously healthy South Asian boy presented to the emergency department (ED) with four days of persistent fever, abdominal pain, vomiting and diarrhea, associated with bilateral non-purulent conjunctivitis, rash over his chest, lower limbs and palms, and red swollen cracked lips. Four weeks prior to presentation, his father tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on nasopharyngeal swab. At the time, the patient was asymptomatic and was not tested. On arrival to ED, he was hypotensive with a blood pressure of 78/47 mm Hg and heart rate of 150 beats/min despite receiving 40 mL/kg of fluid. Peripherally, he was cool to touch and had prolonged capillary refill.

Laboratory results on admission were significant for markedly elevated C-reactive protein (CRP), thrombocytopenia, lymphopenia, hyperferritinemia, hypoalbuminemia, hypertriglyceridemia, elevated liver enzymes, coagulopathy, and markedly elevated troponin I and N-terminal-pro-brain natriuretic peptide (NT-proBNP). An echocardiogram (ECHO) showed reduced left ventricular systolic function and dilated left anterior descending artery. An electrocardiography (ECG) showed diffuse non-specific T-wave abnormalities. The patient's nasopharyngeal swab for SARS-CoV-2 was indeterminate on repeated polymerase chain reaction (PCR) testing, but serology testing for COVID-19 IgG antibody was reactive. He was diagnosed with multisystem inflammatory system in children (MIS-C), also known as pediatric inflammatory multisystem syndrome (PIMS) temporally associated with SARS-CoV-2 and admitted to the intensive care unit (ICU) where he required inotropic support for his cardiac dysfunction. He was given IVIG and steroids as immunosuppressive agents to control his hyperinflammation together with anti-platelet doses of ASA. He improved dramatically requiring only a 4-day hospital stay with the first two in the ICU. He was discharged on a three-week course of weaning steroids with full recovery and no long-term adverse cardiovascular consequences.

At the start of the COVID-19 pandemic, it was thought that most children were either asymptomatic or had mild disease manifestations. Beginning in April 2020, clinicians at COVID-19 epicenters observed the emergence of clusters of school-aged children with fever and features of Kawasaki Disease (KD) and toxic shock syndrome (TSS) following COVID-19 in their communities. Alerts were issued to the medical community and various different names and case definitions were proposed (visit *cps.ca/en/documents/position/pims* for more information).[1] For the purpose of this article, the term MIS-C will be used. This brief update will focus on three practical questions:

1. When to suspect MIS-C?
2. How to approach the diagnostic evaluation of MIS-C?
3. How to treat MIS-C?

When to suspect MIS-C?

The signs and symptoms of MIS-C can largely overlap with Kawasaki Disease and toxic shock syndrome (TSS). KD is a hyperinflammatory syndrome presenting as acute multisystem vasculitis affecting young children. The principal features include: (1) bilateral conjunctival injection; (2) polymorphous skin rash; (3) erythema and edema of the hands and/or feet; (4) cervical lymphadenopathy; and (5) oral mucosal changes, in the presence of at least 5 days of fever. KD is known to have a predilection for the coronary arteries, leading to aneurysm formation in 25% of untreated cases.[2]

Similarly, children with MIS-C present with persistent fevers and multi-organ dysfunction (cardiac, hematologic, gastrointestinal, neurological, renal, and/or dermatologic) usually 3-6 weeks following prior SARS-COV-2 exposure,[3,4] suggesting post-infectious hyperinflammation underlying the pathobiology.[5] Like KD, MIS-C is a syndrome complex with a wide spectrum of clinical phenotypes. A spectrum of COVID-19 associated hyperinflammation syndromes has been proposed[6,7] with three clinical patterns along the hyperinflammation spectrum in MIS-C: Shock, KD, and fever with inflammation, reflecting the continuum of disease severity. Early reports were notable for myocarditis,

Table 1.

Typical Laboratory and Clinical Features in MIS-C

	Organ involvement	Reported Findings in MIS-C
Clinical features	Gastrointestinal	Abdominal pain Nausea/Vomiting Diarrhea
	Cardiovascular	Shock/Hypotension Myocarditis Pericardial Effusion Valvular dysfunction
	Neurologic	Headache Altered Mental Status/ Confusion
	Dermatologic	Rash Oral mucosal changes (erythema and strawberry tongue) Conjunctivitis Red swollen hands and feet
	Renal	Acute Kidney injury
	Respiratory (rare)	Sore throat, congestion, cough, shortness of breath, chest pain, pleural effusion
Laboratory measures	C-reactive protein	↑↑↑
	WBC	↑↑
	Lymphocytes	↓↓
	Neutrophils	↑↑
	Platelets	↓
	Ferritin	↑↑
	Albumin	↓
	Alanine Transaminase (ALT)	↑
	Aspartate Transaminase (AST)	↑
	Sodium	↓
	INR	↑
	PTT	↑
	Fibrinogen	↑
	D-Dimer	↑↑
	Triglycerides	↑
	Troponin	↑
	NT-pro-BNP	↑
Cardiac investigations	Echocardiography	Cardiac dysfunction and coronary artery lesions
	Electrocardiogram	Conduction abnormalities

myocardial dysfunction and overt shock requiring inotropic support as prominent clinical features. Some patients developed coronary aneurysms, as well as macrophage activation syndrome (MAS). It was also observed that MIS-C typically affects healthy children and disproportionately affects non-Caucasian children, with children from African, Hispanic and South Asian ethnicity being more affected. It remains unclear the contribution of environment versus genetics, with higher rates of COVID-19 noted in affected communities.

How to approach the diagnostic evaluation of MIS-C?

A high-index of suspicion for the diagnosis of MIS-C is needed in children living in COVID-19 hotspots, who present with prolonged fever and clinical and laboratory features of inflammation. MIS-C is usually preceded by known SARS-CoV-2 infection in the child or a family member several weeks before presentation. Children may present with features of KD and/or TSS, and often abdominal pain and other gastrointestinal features are prominent. Of note, MIS-C is a diagnosis of exclusion and other causes of febrile illness in children, including other infectious and non-infectious etiologies need to be pursued. Table 1 summarizes the typical laboratory and clinical findings reported in MIS-C. Patients have evidence of a hyperinflammatory state, manifested in laboratory findings of markedly elevated CRP, and measures compatible with viral infection (lymphopenia) and MAS including thrombocytopenia and elevated serum ferritin,[6] which together with hyponatremia, elevated troponin and NT-pro-BNP, are among the worrisome laboratory findings suggestive of a more severe disease phenotype.[8]

How to treat MIS-C?

Although there is rapidly growing literature on MIS-C, management has been largely based on extrapolated knowledge from KD treatment. Several groups have convened expert panels to develop guidance including the American College of Rheumatology (ACR), which developed guidelines for the evaluation and treatment of MIS-C.[8] Children admitted to hospital with MIS-C should be managed by a multi-disciplinary team including rheumatology, cardiology and other subspecialties as needed. The cornerstone of therapy is immunomodulation. Treatment recommended for all children requiring hospitalization for MIS-C involves step-wise progression of immunosuppression, starting with high-dose IVIG (2 g per kg per dose) as first-line therapy. Adjunctive therapy with low-moderate dose glucocorticoid therapy (prednisone 1-2 mg/kg/d) is recommended in patients with severe disease, at high-risk for poor coronary outcome, or as therapy for IVIG failure. In patients who present with critical organ involvement requiring inotropic support, or those who are recalcitrant to IVIG and low-moderate dose steroids, high-dose, pulse glucocorticoids (10-30 mg/kg/d) are recommended. IL-1 blockers, such as Anakinra (> 4 mg/kg/d), may be considered in those with disease refractory to IVIG and steroid therapy, as well as those with features of MAS. Close follow-up with serial laboratory and cardiac assessment will help guide duration and tapering of immunosuppression, with a typical steroid wean over a minimum of 2-3 weeks, and often longer given the high rate of rebound inflammation with quicker tapers.[8] Other immunomodulatory treatments have been used and reported in the literature in-

MIS-C and PIMS *(continued from page 15)*

cluding tocilizumab (IL-6 inhibitor) and infliximab (TNF inhibitor)[9,10] but insufficient data exists for clear recommendations. Similar to KD, MIS-C patients are treated with anti-platelet low dose aspirin (ASA) (3-5 mg per kg per day) as thromboprophylaxis. Anticoagulation with enoxaparin should be considered in MIS-C patients with coronary artery aneurysms as per KD management guidelines and in those with moderate-severe left ventricular dysfunction (Ejection Fraction < 35%).[8]

Serial monitoring of clinical and laboratory parameters, including ECG and ECHO, are recommended as part of the comprehensive follow up post-discharge.

In summary, MIS-C is a post-infectious hyperinflammatory syndrome temporally associated with SARS-CoV-2 infections affecting children. There is a wide spectrum of disease with many sharing features with KD and the most severely affected children presenting with cardiogenic shock and MAS. Immunomodulation is the foundation of therapeutic management, with most children responding rapidly to treatment. MIS-C remains a rare complication of SARS-CoV-2 infection.

References and Suggested Readings:

1. Berard RA, Scuccimarri R, Haddad EM, et al Paediatric inflammatory multisystem syndrome temporally associated with COVID-19. Ottawa: Canadian Paediatric Society; 2020 July 6. Available at *www.cps.ca/en/documents/position/pims*. Accessed February 2021.
2. McCrindle BW, Rowley AH, Newburger JW, et al. 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.
3. Soma VL, Shust GF, Ratner AJ. Multisystem inflammatory syndrome in children. *Curr Opin Pediatr.* 2021; 33(1):152-158. doi: 10.1097/MOP.0000000000000974. PMID: 33278107.
4. Kabeerdoss J, Pilania RK, Karkhele R, et al. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. *Rheumatol Int.* 2021; 41:19–32. https://doi.org/10.1007/s00296-020-04749-4.
5. Henderson LA, Yeung RSM. MIS-C: early lessons from immune profiling. *Nat Rev Rheumatol.* 2021; 17:75–76. https://doi.org/10.1038/s41584-020-00566-y.
6. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine.* 2020; 26:100527. doi: 10.1016/j.eclinm.2020.100527. Epub 2020 Sep 4. PMID: 32923992; PMCID: PMC7473262.9.
7. Yeung RS, Ferguson PJ. Is multisystem inflammatory syndrome in children on the Kawasaki syndrome spectrum? *J Clin Invest.* 2020; 130(11):5681-5684. doi: 10.1172/JCI141718. PMID: 32730226; PMCID: PMC7598074.
8. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. Arthritis Rheumatol. 2020; 72(11):1791-1805. doi: 10.1002/art.41454. Epub 2020 Oct 3. PMID: 32705809; PMCID: PMC7405113.
9. Feldstein LR, Rose EB, Horwitz SM, et al. Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med.* 2020; 383(4):334-346. doi: 10.1056/NEJMoa2021680. Epub 2020 Jun 29. PMID: 32598831; PMCID: PMC7346765.
10. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA.* 2020; 324(3):259-269. doi:10.1001/jama.2020.10369.

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The Schroeder Arthritis Institute: Transforming Arthritis Care Through Research and Education

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The Schroeder Arthritis Institute at the University Health Network in Toronto was launched on October 9, 2020, with a $25 million donation by philanthropists Walter and Maria Schroeder. The Institute is the largest multidisciplinary arthritis hub in Canada and provides a comprehensive approach to the management of bone, joint, spine and connective tissue diseases. The primary goal of the Institute is to provide the best patient care while pursuing a cure, advancing this care across the spectrum of diseases from the clinic to the community.

The Schroeder Arthritis Institute integrates medical, surgical and basic science aspects of four major clinical programs: Hand, orthopedics, osteoporosis and rheumatology. The Institute comprises 46 scientists and clinician-scientists, 113 trainees, and 200 staff. In the past 18 months, investigators at the Institute were supported by over $12M in peer-reviewed research funding and have published more than 400 research articles in peer-reviewed journals.

Created with an integrated vision, a strategic plan developed with broad input, and a sustainable business mo-