Editorial

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) WITH COVID-19

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Pandemic of Coronavirus Disease 2019 (COVID-19) associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is rapidly evolving. As of December 2020, 10.3% of all reported COVID-19 cases in US represents pediatric cases.[1] Most cases in children are asymptomatic or mild cases. Because of this nature, COVID-19 infection in children is under diagnosed. The hospitalization rate of COVID-19 infections in children was 8.0 per 100,000 populations during March 1 – July 25 2020. This number is much lower compared to adult hospitalization rate (164.5 per 100,000).[2] We are still uncertain as to when the pandemic will end. In Indonesia, 9% of COVID-19 confirmed cases are pediatric cases, with 3% mortality rate. There were concerns regarding reports on hyper inflammatory states or Kawasaki-like syndrome in children with COVID-19, the emerging phenotypes are combination of typical/atypical Kawasaki Disease (KD), Kawasaki shock syndrome, toxic shock syndrome and Macrophage Activation Syndrome (MAS).[3] KD itself is an acute systemic vasculitis which was reported first in 1960s by Dr. Tomisaku Kawasaki. Clinical manifestations of Kawasaki-like syndrome are fever, conjunctival injection, skin rash, edema of the extremities, and swollen lymph nodes.[3]

On April 2020, physicians in the United Kingdom and France identified an outbreak of children admitted to the paediatric intensive care unit with a hyper inflammatory condition characterized by fever, cardiovascular shock, and suspected Severe Acute Respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection, later on this was referred as Paediatric Multisystem Inflammatory Syndrome–temporally associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C).[4] This condition has several spectrums, including Kawasaki-like disease, Kawasaki disease shock syndrome, toxic shock syndrome, myocarditis, and MAS.[5] MIS-C often manifested after the infection. Thus, evidence suggests that this disease is immunologically mediated.[6] Even though the pathogenesis, clinical manifestation, and outcomes of MIS-C are still unknown, MIS-C can lead to shock and multiple organ dysfunction. The Centre for Disease Control and Prevention (CDC), Royal College of Pediatrics and Child Health, and World Health Organizations came up with different case definition (Table 1).[7-9] These case definitions are problematic since some cases that are not MIS-C (including Kawasaki-like syndrome) fulfil the definitions of MIS-C.

Given the novelty of MIS-C, there are no widely accepted evidence-based guidelines for management of children with MIS-C yet. [10-11] Several centers and organizations have created and published their own guidelines to guide hospital evaluation and management thus early reports of MIS-C highlight the variability in the evaluation and management of these patients.[10-12] Most reported MIS-C cases were treated using the standard protocol for KD which is intravenous immunoglobulin (IVIG) with or without aspirin (aspirin was commonly recommended for mild cases).[5, 6, 10-13] IVIG was the most widely recommended medication to treat MIS-C (98% of centers include IVIG in their recommendations), with 60% of centers recommend the use of IVIG regardless of severity and 21 of the 39 protocols that mentioned any use of IVIG recommend a second dose of IVIG for cases that were refractory to the first dose.[11, 14] Steroids have also been used to treat MIS-C and were listed in 93% of protocols primarily for moderate or severe cases.[10, 11] Corticosteroid therapy is usually an addition for those with shock or at greater risk of coronary artery aneurysm along with IVIG and aspirin as the initial treatment.[6] IVIG or corticosteroids or both were given to most patients for anti-inflammatory and antibody-

mediating effects.[13] A large diversion from the KD guidelines was the inclusion of systemic anticoagulation in some MIS-C protocols where heparin or low molecular weight heparin was used primarily in severe cases (elevated d-dimmers and MIS-C cases with thrombosis).[11]

Two-thirds of MIS-C cases were admitted to the PICU.[5, 14] Most of MIS-C cases required vasopressor support and some invasive mechanical ventilation and mechanical circulatory support.[5, 13, 14] Through special care and aggressive treatment paediatric patients have shown favourable outcomes.[10] Most of those who had dilated coronary arteries healed as usual in a short time.[5] Patients had rapid clinical improvement and reduction in inflammatory markers with the frequently used therapies (IVIG and corticosteroids).[6, 14] The reported case fatality rate from various countries is relatively low.[5, 12] The group which had symptoms and signs of respiratory system involvement had higher mortality.[5] Studies found the death rate was 1.7-1.8%.[14] It is comparable to that observed in adults with severe COVID-19 between the ages of 55-64 years, which is 1-3%.[14] While relatively low, it is much higher than the 0.09% mortality rate observed in children with COVID-19. In general the prognosis for MIS-C patients is relatively good and recovery occurs fast.[5]

Indeed, diagnostic criteria of MIS-C are still developing as we know it.[10] Despite different clinical presentation, MIS-C shares common feature in terms of cytokine storm leading to hyper inflammation and hypercoagulable state. Current hypothesis proposes MIS-C to be linked with COVID-19, although the association has yet to be proven. Since it shares common ground with toxic syndrome, MAS/secondary HLH and KD, the principle of treatment largely depends on the clinical and laboratory findings according to its phenotype. Steroid mainly to suppress pathologic hyper inflammation, IVIG to neutralize complement and autoantibody, as well as to stimulate Regulatory T Cells(Treg), IL-1ra receptor antagonist (anakinra) in case of MAS, aspirin to prevent hypercoagulable state, and heparin if any evidence of DIC.

As mentioned above, the characteristics and definitions of MIS-C are still discordant.[10] However, they do share the same features of hyper inflammation and hypercoagulation, which are intriguingly similar as those found in septic patients. Previous studies have reported that hyper inflammation found in sepsis shared three different phenotypes with one common pathway of MAS.[15] It is well established that MIS-C patients experienced cytokine storm and hyper inflammation, characterized by marked increase in C-reactive protein (CRP), ferritin, and IL-6. In addition, d-dimmer levels often increased which indicate coagulation disorder as those found in MAS.[14] Although pathogenesis study of MIS-C is still undergoing worldwide, these shared features might possibly help in a more targeted therapy.

Just like in other countries who have reported, MISC is also found in Indonesia. There is currently lack of data regarding MISC as different centers still have discrepancy in terms of diagnostic criteria for MISC, as well as limited laboratory testing in non-teaching hospitals. We believe that the actual number of MISC in COVID-19 affected children is higher, however submerged by the low testing and tracing capacity in Indonesia. MISC is a new entity, yet important to diagnose and treat accordingly.

Reflecting at the first few cases reported, MISC phenomenon reminded us about the classic Indian tale of "Six blind men and the elephant". What we know and believe is only what we have seen and experienced. However, the most prudent course of action is to have a bird's eye view. Nevertheless, it is still challenging as what we have discovered about MISC is merely the tip of the iceberg. We hope to look forward into more discoveries to help improve our understanding of MISC phenomenon and its therapeutic target. Furthermore, there is also a need for simpler clinical/laboratory criteria to better MISC cases finding which can be most useful in developing countries.

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Table 1. Case definitions of MIS-C

	MIS-C associated with COVID-19	MIS-C associated with COVID-19	PIMS-TS
Organisation/ Publication	CDC	WHO	Royal College of Paediatrics and Child Health
Age	< 21 years	0-19 years	Child (age not specified)
Inflammation	Fever (≥ 38.0°C or subjective fever for ≥ 24 hours) and elevated inflammatory markers	Fever ≥ 3 days and elevated markers of inflammation	Persistent fever >38.5°C and elevated inflammatory markers
Main features	Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and no alternative plausible diagnoses; and	Two of the following: 1) rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet), 2) hypotension or shock, 3) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), 4) Evidence of coagulopathy (by PT, PTT, elevated d-dimmers), 5) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting).
SARS-CoV-2 status	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within 4 weeks prior to the onset of symptoms.	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	RT-PCR positive or negative
Exclusion	No alternative plausible diagnoses	Other microbial cause of inflammation	Any other microbial cause