A review of multisystem inflammatory syndrome in children (MIS-C) related to COVID-19

Carlson Kurniawan

INTRODUCTION

We have been dealing with the global pandemic of Coronavirus Disease 2019 (COVID-19) since December 2019. It is caused by SARS-CoV-2, a novel virus first reported in Wuhan that can cause severe acute respiratory symptoms. On 26th November 2020, there are more than 59 million confirmed cases of COVID-19 and over 1.4 million deaths according to WHO. As 10th August 2020, data from Indonesian Pediatric Society reported more than 3900 cases and 59 deaths, which it is the highest in Asia.1-5

Severe lung involvement also followed by respiratory failure is the most common complication in adults, but it can affect multiple organs too.9 Typically the disease peaks during the second week of illness. Most children have mild symptoms and usually don’t need any intervention. But in the past several months, there have been increasing reports describing children and adolescents with COVID-19-associated multisystem inflammatory conditions, which develops not on the acute stage but after the infection.1 This condition is called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C). These cases’ clinical features are similar to Kawasaki disease. It can lead to shock and multiple organ failure which can be fatal and have long term side effects. Case definitions for MIS-C can be seen on Figure 1.1,3,6,7

A new disease?

Coronaviruses are a family of positive-sense single-stranded RNA viruses. Different genera of coronavirus are known (alpha, beta, delta and gamma). Since the outbreak of SARS-CoV-2, numerous reports of children with presenting features of systemic inflammatory disease mimicking Kawasaki disease are reported and it is associated with SARS-CoV-2 infection and it was mentioned as Kawasaki disease.8-10

Kawasaki disease (KD) is an acute febrile, mucocutaneous lymph node syndrome with medium and small-sized vessel vasculitis affecting children under 5 years old. The main complication includes coronary dilatation and aneurysm (up to 40% if not treated). Other concerning conditions are pericarditis and myocarditis, which can lead to cardiogenic shock.4 Numerous studies and reports have been published and highlighting this condition. Even so, the etiopathogenesis remains unknown. Presumably, host’s immune response against infection is associated with the pathophysiology.9-10

Perspective on Immunology

The rapid spread of the virus has been very concerning globally, over 59 million confirmed cases have been reported. However, the infection rate in children is much lower than adult. Numerous cases of hyper inflammation have been reported. The viral spike protein of SARS-CoV-2 is presumed can trigger the cytokine storm. Viral sequences were compared between children with MIS-C and children without MIS-C, but still inconclusive and needed further studies.4,9,10

Angiotensin-converting enzyme 2 (ACE2) was identified as the receptor of SARS-CoV-2, it has to bind to ACE2 before entering hosts’ cell. ACE2 has protective effect in the lung and may be a target for therapy of ARDS in COVID-19.11 Lymphopenia, thrombocytopenia, elevation of inflammatory markers are the most common laboratory findings. One study stated majority of patients showed...
Clinical Features, Outcomes and Treatments

MIS-C closely resembles Kawasaki disease and can be challenging to distinguish between these two conditions in a patient. Kawasaki clinical criteria can be used and it was studied and compared on numerous studies.1,7,8,14

Common clinical findings including fever, abdominal pain, skin rashes, conjunctivitis/cheilitis, diarrhea, mucous membrane changes, headache, respiratory symptoms, lymphadenopathy, swollen hands and feet, sore throat, confusion, hemodynamic changes (tachycardia/arrhythmia, hypotension, lowered left ventricular ejection fraction), hypercoagulable state (elevated D-dimer) and elevated inflammatory markers such as CRP, Procalcitonin, Fibrinogen and Neutrophils.15-17

Most common clinical outcomes are acute kidney injury, inotropic support, intubation, extracorporeal membrane oxygenation (ECMO), coronary artery aneurysm and even death.17

Children with MIS-C who developed shock had higher inflammatory markers including higher CRP and neutrophil counts, lower albumin, lower lymphocyte and elevated troponin and NT-pro BNP. The main treatment of this condition is to reduce the inflammation, because it is mainly compromise the cardiovascular system, vasopressor supports are needed and low dose of aspirin (3-5 mg/kg/day, maximum 81 mg/day) can help to reduce incidence of coronary artery disruption. Hypercoagulable state, endothelial injury, stasis from immobilization, dysfunction of ventricle can be seen in MIS-C, so it was recommended to give antiplatelet and/or anticoagulation medication.12,16,17

Smaller fluid boluses (10 m/kg) should be administered in patient with suspected ventricular dysfunction.18 Immunomodulatory therapy can be beneficial, such as intravenous immunoglobulins (high dose of 2 gr/kg, based on ideal body weight), low dose methylprednisolone (1-2 mg/kg/day) or pulse dose (10-30 mg/kg/day) can be used if not responsive and biologic drugs (tocilizumab, anakinra, infliximab) can be considered in critically ill children. However, only anakinra (>4 mg/kg/day IV or SC) is recommended by American College of Rheumatology for cases with refractory state.10,16

Immunomodulatory therapy can be beneficial, such as intravenous immunoglobulins (high dose of 2 gr/kg, based on ideal body weight), low dose methylprednisolone (1-2 mg/kg/day) or pulse dose (10-30 mg/kg/day) can be used if not responsive and biologic drugs (tocilizumab, anakinra, infliximab) can be considered in critically ill children. However, only anakinra (>4 mg/kg/day IV or SC) is recommended by American College of Rheumatology for cases with refractory state.10,16

Role of antiviral therapy (e.g. remdesivir) is still cannot be recommended, because MIS-C happened in post-infection stage, not on the acute phase of the disease.12,18 Many vaccine candidates are being developed now, mostly targeting S-protein of SARS-CoV-2, preliminary study has shown promising results for the efficacy and safety profile (Figure 3).19
CONCLUSION

MIS-C is a syndrome related to SARS-CoV-2 infection with presentations resembling Kawasaki disease. It was mainly caused by the hyperinflammation triggered by the viral spike and happened during the post-infection stage. Though the pathogenesis remains unclear, numerous studies have been done and reported disrupted immune responses lead to multisystem organ failure, especially cardiovascular system. Modulating the immune response is the main therapy for this condition combined with fluid restriction, vasopressor, antplatelet/anticoagulation agent and biological agent such as anakinra.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

FUNDING

None.

REFERENCES

7. Girmaud M, Starck J, Levy M, Marais C, Chareyre J, Hraiche D et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in...


