REVIEW

Intisari Sains Medis 2022, Volume 13, Number 3: 670-673
P-ISSN: 2503-3638, E-ISSN: 2089-9084

Intisari Sains Medis

Published by Intisari Sains Medis

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

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Received: 2021-12-29
Accepted: 2022-06-18
Published: 2022-12-01

ABSTRACT

Global pandemic of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel virus which first reported in Wuhan in December 2019. It can cause severe respiratory conditions including respiratory failure. Different from adults, children usually have milder symptoms of the disease. A post-infection complication that involves multisystem organ failure in children is reported in numerous countries. It is mentioned as multisystem inflammatory syndrome in children (MIS-C) or Kawa-COVID-19, because it resembles Kawasaki Disease. The pathogenesis remains unclear, but it is presumed that hosts' innate immune response triggered the condition. Modulating the immune response is the main target of the therapy. High doses of intravenous immunoglobulins, low doses of corticosteroids (methylprednisolone), anti-IL-1 (anakinra), antiplatelet such as aspirin can be used to treat MIS-C. Antiviral therapy is not proven to be effective and other immunomodulatory agents still needed further studies.

Keywords: COVID-19, inflammatory, multisystem, MIS-C.
Cite This Article: Kurniawan, C. 2022. A review of multisystem inflammatory syndrome in children (MIS-C) related to COVID-19. *Intisari Sains Medis* 13(3): 670-673. DOI: 10.15562/ism.v13i3.866

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.[3] Typically the disease peaks during the second week of illness. Most children have mild symptoms and usually doesn'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 Kawa-COVID-19.[6-8]

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.[8]

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.[6,8]

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

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous 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, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Figure 1. Case definitions of MIS-C.[17]

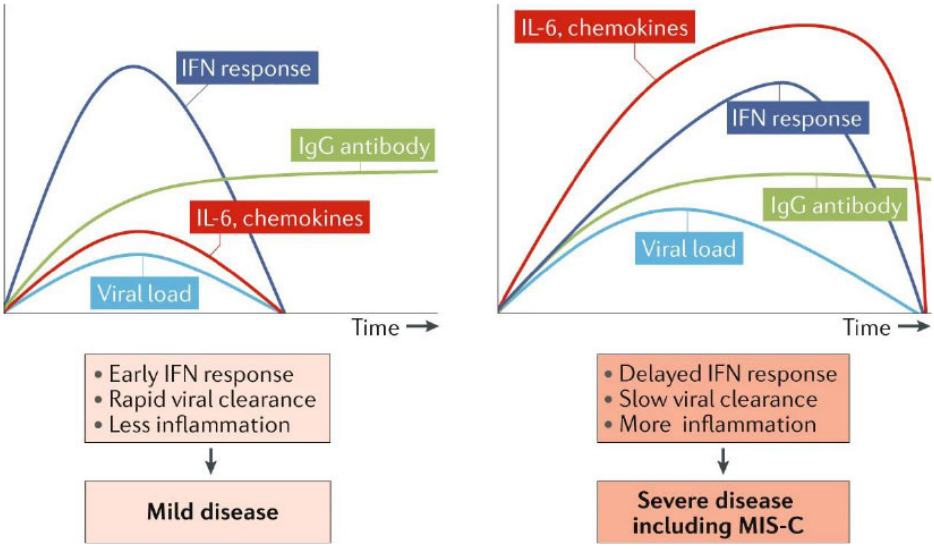

Figure 2. Pathogenesis of MIS-C: a hypothesis.[20]

reduced number of CD4, CD8 and NK cells. Elevation of IL-6 and Il-10 and sIL2R were also discovered in MIS-C.[1,11–13] Evidence has shown dysregulated innate immune response, cytokine storm and endothelial damage play a role in severe cases. Neutrophils are the major component of innate immune response, the mechanism is called neutrophil extracellular traps (NETs). If stimulated with viral infection, it can trigger hyperinflammation response which it can be seen on MIS-C. From this finding, the management of this condition mainly immunomodulatory therapy such as intravenous immunoglobulins (IVIG) and corticosteroids (Figure 2).[1,2,13]

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.[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 (can be seen in Figure 3).[12,16] 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]

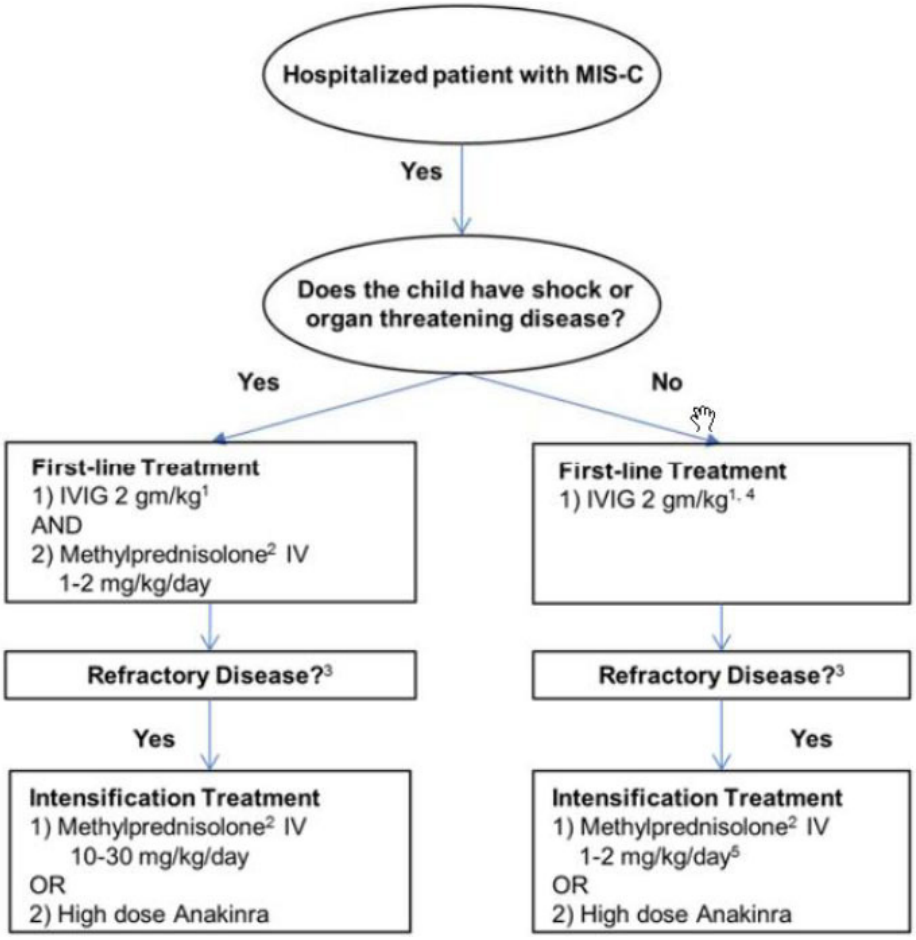

Figure 3. Algorithm for treating MIS-C.[21]

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, antiplatelet/anticoagulation agent and biological agent such as anakinra.

AUTHOR CONTRIBUTIONS

The authors contributed to the preparation, drafting, and writing of this review.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

FUNDING

None.

REFERENCES

1. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20:e276–e288.
2. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest. 2020;130:5967–5975.
3. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383:334–346.
4. WHO. Coronavirus disease (COVID-19) pandemic [Online]. 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQiAwf39BRCCARIsALXWETz0pQrR9PO5BqXG6NmAh2zjg0DG-GeCl4eNea0no80qqHMQdSBEtqwaAl0kEALw_wcB (accessed 26 Nov2020).
5. Pranita E. High icidens of COVID-19 in child in Asia, what are the cause? [Online]. 2020. Availavle at: https://www.kompas.com/sains/read/2020/10/02/163000323/infeksi-covid-19-pada-anak-indonesia-tertinggi-di-asia-apa-sebabnya-?page=all (accessed 26 Nov2020).
6. Ebina-Shibuya R, Namkoong H, Shibuya Y, Horita N. Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19: Insights from simultaneous familial Kawasaki Disease cases. Int J Infect Dis. 2020;97:371–373.
7. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
8. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999–1006.
9. American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. 2020.https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/ (accessed 26 Nov2020).
10. Pang J, Boshier FAT, Alders N, Dixon G, Breuer J. SARS-CoV-2 Polymorphisms and Multisystem Inflammatory Syndrome in Children. Pediatrics. 2020;12:e2020019844.
11. Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacol Res. 2020;157:104833.
12. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H 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;72:1791–1805.
13. Lee PY, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. J Clin Invest. 2020;130:5942–5950.
14. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH et al. Recognition of a Kawasaki Disease Shock Syndrome. Pediatrics. 2009;123:e783–e789.
15. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in

critically ill children. Ann Intensive Care. 2020;10:69-75.
16. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. Pediatr Cardiol. 2020;41:1391–1401.
17. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020;324:259–269.
18. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307-322.
19 Kim K-D, Hwang I, Ku KB, Lee S, Kim S-J, Kim C. Progress and Challenges in the Development of COVID-19 Vaccines and Current Understanding of SARS-CoV-2- Specific Immune Responses. J Microbiol Biotechnol. 2020;30:1109–1115.
20. Rowley AH. Understanding SARS-CoV-2 related multisystem inflamatory syndrome in children. Nat Rev Immunol. 2020;20:453-454.
21. American College of Rheumatology. Clinical guidance for pediatric patient with multisystem inflamatory syndrome in children (MIS-C) associated with ARS-CoV-2 and gyperinflammation in COVID-19 [Online]. 2020; Available at: https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflamation.pdf.