

Conference Paper

Clinical Characteristics of Multisystem Inflammatory Syndrome in Children With Severe and Critical Symptoms in the Pediatric Intensive Care Unit

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Abstract.

Generally, children infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV-2) have mild symptoms or are asymptomatic. However, some children have severe and critical symptoms affecting several organ systems, including the gastrointestinal, cardiovascular, respiratory, and neurological systems. These severe and critical symptoms are associated with multisystem inflammatory syndrome in children (MISC). This study aimed to describe the clinical features, ventilation modalities usage, and outcome conditions of these children. This was a retrospective study of children with COVID-19 and MISC who were treated in the COVID-19 isolation pediatric intensive care unit (PICU) of Saiful Anwar General Hospital over one year. The data were obtained from medical records and were analyzed descriptively. A total of 491 pediatric patients with suspected COVID-19 were included; 51 had a confirmed COVID-19 diagnosis; 9/491 (1.8%) were patients with MISC who were treated in the PICU; and 7/9 (78%.0) of MISC patients in the PICU used mechanical ventilators. The frequency of MISC patients with gastrointestinal problems was 7/9 (78%) patients, respiratory problems was 9/9 (100%), and myocardial injury (increased troponin) was 5/9 (56%) patients. All MISC patients admitted to the PICU experienced shock with vasoactive drugs including dobutamine, epinephrine, norepinephrine and vasopressin. All MISC patients with severe and critical symptoms had comorbidities. Invasive mechanical ventilation was provided for 7 patients, and 2 patients received non-invasive ventilation. The mean of PEEP used in the invasive ventilation was 7-9 cmH₂O. The length of the ventilator usage was 2-21 days, with 2 patients passing away, both with a comorbidity and multiorgan system injuries. It can be concluded that pediatric patients with confirmed COVID-19 may also have MISC with severe and critical symptoms. Early recognition of pediatric patients with MISC is necessary to reduce morbidity and mortality.

Keywords: COVID-19, multisystem inflammatory syndrome, children

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1. Introduction

The spread of Covid-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV-2) is very fast so that it has a very wide multidisciplinary effect throughout the world [1][2]. On September 13, 2021 WHO reported that 224,511,226 of the world's population were confirmed to have Covid-19 with 4,627,540 people died [3]. In Indonesia, there were 4,167,511 confirmed cases of Covid-19 with 138,889 people dying. The prevalence of pediatric patients aged 0-18 years who have confirmed Covid-19 is 13% from total cases with 1% fatality [4]. Meanwhile, the prevalence of children experiencing Covid-19 in the world is <5%, with a mortality rate of <0.1%. The mortality rate of children who have Covid-19 is lower than adult patients [5][6].

Since April 2020, several European and North American countries have reported a number of patients experiencing severe multisystem inflammatory syndrome with characteristics similar to Kawasaki disease (KD) or Toxic Shock Syndrome. The patient is in shock and multiorgan failure. This symptom is often called Multisystem Inflammatory Syndrome in Children (MISC). MISC in some children can cause severe and critical symptoms that require treatment in the PICU [7][8]. The patient is diagnosed with MISC based on a positive test result for reverse transcription-polymerase chain reaction (RT-PCR) or antibody test for COVID-19 or has a history of recent contact with a COVID-19 patient [9]. There are not many studies on MISC in pediatric patients with severe and critical symptoms in Indonesia, therefore this study aims to describe the clinical characteristics of MISC patients with severe and critical symptoms who are treated in the PICU.

2. Methods

A retrospective study was conducted on pediatric patients with severe and critical MISC who were admitted to the PICU. The data recorded included age, gender, weight, organ system involvement, presence or absence of comorbidities. In addition, this study also noted the presence of cardiovascular disorders, hemodynamic instability, use of vasoactive drugs, mode and duration of ventilator use, maximum ΔP , PEEP, and the patient's outcome. The study was conducted in the COVID-19 isolation PICU, Saiful Anwar General Hospital from April 2020 to April 2021. The inclusion criteria were children aged 0-18 years diagnosed with MISC based on WHO criteria. The exclusive criteria were septic shock and incomplete data. The consecutive sampling was used this study. Results are descriptive and presented as absolute numbers and percentages,

analyzed by Ms. Excel software. Ethics approval has been obtained from the Health Research Ethics Commission, Dr. Saiful Anwar Hospital, Malang, Indonesia, with number 400/123/K.3/302/2021 before the study was conducted.

3. Results

Pediatric patients were suspected Covid-19 in 1 year as many as 491 patients and 51 patients confirmed Covid-19, 9/491 (1,8%) patients with MISC were treated in the PICU room, male 5/9 (55,5%), the age range of MISC patients was 41 days to 16 years and 7/9 (78%) MISC patients in the PICU were using mechanical ventilators. The frequency of MISC patients with gastrointestinal problems was 7/9 (78%) patients, respiratory problem 9/9 (100%) as seen as in Table 1. Myocardial injury (elevated troponin) occurred in 5/9 (56%) patients and all MISC patients admitted to the PICU were in shock. Vasoactive drugs used are dobutamine, epinephrine, norepinephrine, vasopressin. All MISC patients with severe and critical symptoms had comorbidities. Invasive mechanical ventilation was applied to 7 patients, and 2 patients received Non-Invasive Ventilation (NIV). The average maximum ΔP and PEEP using invasive ventilation was 10-14 cm H₂O and 7-9 cmH₂O. The duration of ventilator use was 2-21 days, with 2 patients dying, both with comorbidities and multiorgan system injuries as seen as Table 2.

TABLE 1: Demographic Characteristics, Organ System Involvement, and Comorbidity from Children with MISC Isolation PICU.

Demographic Characteristics	Organ System Involvement	Comorbid	Case Age	Gender
Body Weight (kg)	Gastrointestinal Tract (GIT)	Cardiovascular	Respiratory	Hematology
Yes	No	Case 1	43 days	Male
3.5	Case 2	13 months	Female	5.5
Case 3	16 years	Male	71	Case 4
9 years	Male	18	Case 5	41 days
Male	4,1	Case 6	13 years	Female
29	Case 7	11 years	Male	36
Case 8	7 years	Female	21	Case 9
8	Tahun	Female	2	

TABLE 2: Mechanical Ventilation Characteristics of the Children with MISC who Receive Mechanical Ventilation on Isolation PICU.

Demographic Characteristics				Type of Mechanical Ventilation		Length of ventilation (Days)	P Control max	PEEP max	Outcome	
Case	Age	Gender	Body Weight (kg)	Invasive	Non Invasive				Survive	Not Survive
Case 1	43 days	Male	3.5			7 days	14	9		
Case 2	13 months	Female	5.5			21 days	12	9		
Case 3	16 years	Male	71			2 days	12	7		
Case 4	9 years	Male	18			15 days	10	8		
Case 5	41 days	Male	4,1			6 days	11	7		
Case 6	13 years	Female	29			15 days	12	7		
Case 7	11 years	Male	36			3 days	10	7		

4. Discussion

Most of the symptoms COVID-19 in children are asymptomatic and mild. Children with Covid-19 who experience critical clinical symptoms and require critical care are 2%. Several studies reported that 8% of children suffering from Covid-19 were admitted to the PICU and 4% needed mechanical ventilation (10)(11)(12). Some of the Covid-19 pediatric patients who experience severe and critical symptoms have clinical symptoms of hyperinflammatory shock similar to atypical Kawasaki Disease, Kawasaki Disease Shock Syndrome or Toxic Shock Syndrome. This condition is known as Multisystem Inflammatory Syndrome in Children (MISC) (13). At the beginning of the pandemic, in Indonesia there were still not many MISC cases, in addition to the difficulty of diagnosing Covid-19 in children because the clinical and laboratory features of pediatric patients with Covid-19 were not typical and the PCR-RT examination at that time was still not many, and typical symptoms MISC has not been found much. But after that in Indonesia also found cases of MISC (14).

The criteria for the diagnosis of MISC according to WHO are children and adolescents 0–19 years of age with fever > 3 days and two of the symptoms rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet), hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), evidence of coagulopathy (by PT, PTT, elevated d-Dimers), acute gastrointestinal problems. And elevated markers of inflammation, 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 (15). In our study, 9 patients out of 491 suspected Covid-19 patients had MISC and 78% had gastrointestinal problems. Gastrointestinal problems were also reported in 8 (100%) MISC patients in the United Kingdom and 6 out of 10 MISC patients in Italy (13)(15)(16). Gastrointestinal problems in MISC patients are thought to be due to excessive inflammation, this can be evidenced by an increase in inflammatory markers. Gastrointestinal symptoms are also mimicking those of GI infection or inflammatory bowel disease, therefore it is necessary to distinguish between comorbidities and extreme elevations of inflammatory markers (17). Gastrointestinal symptoms associated vasculitis induced bowel wall edema or ischemia, cardiac dysfunction and/or shock, mesenteric lymphadenitis and mesenteric inflammation (18).

In our study 100% of patients experienced respiratory problems and 78% used mechanical ventilation. Respiratory problems, apart from being caused by pneumonia,

can also be caused by pulmonary embolism. The clinical characteristics of MISC patients are similar to those of adult patients with COVID-19 with severe clinical symptoms. Both have signs of inflammation characterized by an increase in inflammatory markers, an increase in ferritin, fibrinogen, d-dimer and IL-6. When referring to adult patients who experience Covid-19 with severe symptoms, they often show an increase in d-dimer and C-reactive protein. This situation increases the risk of pulmonary embolism when compared with patients without an increase in inflammation. This is consistent with the situation that occurs in pediatric patients with MISC. The high elevation of inflammatory markers in MISC patients may predispose to pulmonary embolism (19).

Patients using mechanical ventilation in this study were 78%, when referring to The Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) and the section of respiratory failure from the European Society for Pediatric and Neonatal Intensive Care (ESPNIC), the recommendation for the use of mechanical ventilation for pediatric patients with Covid-19 are Continuous Positive Airway Pressure (CPAP) or Bi-Level Non-Invasive Ventilation (NIV) as the first choice of oxygen therapy in COVID-19 children with ARDS (SpO_2/FiO_2 between 221 to 264). CPAP or Bi-Level NIV is recommended over High Flow Nasal Cannula (HFNC). HFNC was considered if there was no CPAP/Bi-level NIV and the patient still had $SpO_2/FiO_2 > 264$ ($FiO_2 < 0.35-0.4$). Intubation is mandatory if SpO_2/FiO_2 is less than 221 and in patients with refractory respiratory distress (no improvement after oxygen therapy with CPAP/NIV with a target SpO_2 of 92-97% and $FiO_2 < 0.6$ for 60-90 minutes). The initial recommendation for the use of PEEP in invasive ventilation for patients who have respiratory failure or patients who have failed to use non-invasive ventilation, PEEP starts from 10 cmH₂O and can be increased gradually if needed. Then there was an updated recommendation in 2021 from ESPNIC stating that the PEEP recommendation starts at 8-10 cmH₂O and can be increased. In our study, the PEEP used was 7-9, lower than the ESPNIC recommendation, with patient outcome 2 out of 9 patients dying (20)(21). Patra-Barbosa et al. reported that the maximum PEEP used in patients with MISC was 12 cm H₂O (22). Fisler G et al. also reported that the highest use of PEEP in pediatric patients with Covid-19 was 12 cm H₂O (23). The use of different PEEP, in our opinion, is individual according to the circumstances of each patient. Carvalho et al. also suggested that the PEEP setting is determined by lung elasticity and compliance. Low PEEP is recommended in patients with low lung elasticity and high lung compliance patients (24). The maximum PEEP in our patients is lower than the ESPNIC recommendation, it is very likely that our patients still have high lung compliance. Another study in Argentina also recommended the use of PEEP based on the type of lung damage. In patients with low compliance, the

recommended PEEP used is 10-14 cmH₂O with a tidal volume of <6 ml/KgBW, while in patients with high compliance the PEEP recommendation used is PEEP 8-10 cmH₂O with a tidal volume of 6-9 mL/KgBW (25).

One of the clinical manifestations of MISC is hypotension or shock. A report from the UK, at the time of initial finding of MISC cases, found that 8 (100%) MISC patients experienced vasoplegic shock that was refractory to fluid resuscitation and required hemodynamic support in the form of vasoactive drugs, namely noradrenaline and milrinone (13). One option for monitoring fluid adequacy in shock patients is to measure SVV using a non-invasive hemodynamic monitoring tool. If during monitoring hemodynamic the patient is found to be refractory to resuscitation fluids, it is necessary to consider the use of vasoactive drug (26). The same situation was found in our study, all MISC patients were in shock and required vasoactive drugs such as dobutamine, epinephrine, norepinephrine, and vasopressin. Patients who experience MISC in several studies experience multiorgan failure in the form of neurologic, cardiogenic or vasoplegic shock (27). In MISC, some physiological aspects are similar to Kawasaki Shock Syndrome, but in MISC left ventricular systolic dysfunction is found in almost all patients who experience a decrease in systolic blood pressure. In our study, in addition to all patients experiencing shock, 56% of patients also experienced myocardial injury (elevated troponin enzymes). Acute myocardial injury in SARS-CoV-2 infection has been reported in the adult population at the start of the pandemic. Manifestations of myocardial injury in patients with SARS-CoV-2 infection, including fulminant myocarditis, decreased ejection fraction, and increased myocardial enzymes (28). According to Angurana S.K. et al. in MISC patients who went into shock, had higher leukocyte values than MISC patients who did not experience shock. In addition, patients who experience shock also develop myocardial dysfunction. Myocardial disorders include LEVF <55% (50–70% children), myocarditis (50–80%), coronary artery dilatation or aneurysm (6–20%) and residual myocardial dysfunction at discharge (2–18%). Shock that occurs in MISC patients is caused by multifactorial factors, including myocardial dysfunction, vasoplegia and vasculitis (18). In our study, all patients had comorbidity and several organ system injuries, worsening the outcome.

Our study has limitations, the number of pediatric Covid-19 patients with MISC is relatively small and the study was only conducted in one hospital. However, with this study, we believe it can contribute to understanding cases of MISC with severe and critical symptoms. We conclude that the problem in MISC is very complex, because the patient can have multiorgan failure, therefore early recognition of severe and critical symptoms in MISC is expected to reduce mortality and morbidity.

5. Conflict of Interest

None of author have a conflict of interest to declare.

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