EDITORIAL

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The difficulty of establishing the diagnosis of pediatric COVID-19 in Indonesia

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The Covid-19 pandemic has not shown any signs of ending soon. Until May 1, 2020, the latest data recorded that Covid-19 cases in the world have reached 3,336,680 cases, with 235,245 people died and 1,054,786 people recovered. Of the number of still-active cases, 98% are mild cases, while the remaining 2% are severe. Since it was first identified (December 2019) until it was announced as a pandemic on March 11, 2020), cases of children have not escaped the effects of infection.

This Coronavirus is not the first time virus which appeared. Before the emergence of SARS-COV2 (Severe Acute Respiratory Syndrome Coronavirus 2), SARS-COV, Betacoronavirus group 2B also caused the SARS outbreak (2002) in Guangdong Province, southern China. SARS-COV, which was caused by Betacoronavirus group 2B, spread to Hong Kong and many other countries. The dominant clinical symptom in SARS-COV patients in 2002 was a severe infection of the lower respiratory tract. The number of disability (morbidity) and mortality rate (mortality) is relatively high. More than 8000 people became infected, and 774 people died in 28 infected countries. Cases in children themselves are predominantly (50-80%) obtained from family members of the child. The clinical symptoms of children infected with SARS-COV were fever (91-100%), and some were asymptomatic (2%). Fortunately, it is feared that children are a vulnerable group to severe infections; even death does not occur.

The Coronavirus has the ability to mutate and recombine faster so that it can easily spread from animals to humans. Another outbreak caused by the novel Coronavirus is the Middle East Respiratory Syndrome Coronavirus (MERS-Cov), which emerged in Saudi Arabia in 2012. This virus is known to be transmitted from camels to humans. MERS-Cov that occurred in Saudi Arabia was also caused by a new Betacoronavirus group, namely group 2C. This virus also causes infections of the lower respiratory tract and causes a mortality rate of 20-40%. Apart from being endemic to the Middle East, a nosocomial outbreak of MERS-CoV also occurred in South Korea in 2014. This outbreak involved 16 hospitals and 186 patients; this was caused by a doctor who returned from the Middle East. MERS-CoV has spread to 27 countries and is estimated to cause 2494 infections and 858 deaths. How is MERS-CoV infection in children? Clinical symptoms of children infected with MERS-Cov 32% are asymptomatic, and the child mortality rate reaches 6%.[1]

In the case of Covid-19, the percentage of children being infected is still relatively small. In addition to small infection cases, clinical symptoms in children are often mild-moderate, severe clinical symptoms are rarely found. A report from Jacqueline S. M. Ong et al., found that cases of confirmed Covid-19 in children under 19 years of age only reached 2%, while in Italy, cases of children confirmed by Covid-19 only reached 1.2%. This situation is slightly different from in Korea, where children aged less than 19 years who were authorized to have Covid-19 were found to be 4.8%.[2]

The thing that distinguishes the condition of children infected with Covid-19 compared to adults is clinical symptoms. Children tend to have milder symptoms than adults. A clinical and epidemiological study conducted by Haiyan Qiu et al., in Zhejiang, China, on children with Covid-19, found that 89% of children infected with Covid-19 were transmitted from other family members. Also, 47% of children had mild clinical symptoms, and the rest had moderate clinical signs and were asymptomatic. The age of children who fall into severe and critical clinical conditions has not been obtained. The symptoms most often experienced by children infected with Covid-19 are fever and dry cough. Other signs that rarely occur in children are runny nose, painful swallowing, shortness of breath, vomiting, or diarrhea. How is the data in Indonesia?

There is still no official data in Indonesia regarding the number of Covid-19 sufferers based on age groups. This is probably due to the ongoing pandemic, so the data is still incomplete.[3] One hypothesis that explains the clinical symptoms of Covid-19 is the role of the Angiotensin-converting Enzyme (ACE-2) receptor. The ACE-2 receptor is the attachment site for the SARS-CoV virus, which caused the SARS outbreak in 2002. Several studies

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have also found that SARS-COV-2 has amino acids that are homologous to the amino acids in SARS-CoV. This is why experts suspect that the ACE-2 receptor is also an attachment site for SARS-CoV 2, which causes Covid-19 infection.

ACE-2 receptors have a protective function in several organs such as the lungs, kidneys, heart, gastrointestinal tract, and blood vessels. However, if SARS CoV-2 occupies the ACE-2 receptor, there will be dysfunction in some of these organs. The expression of ACE-2 receptors increases in adults, and in people with Diabetes Militus, some Diabetes Militus patients infected with Covid-19 have a more severe clinical condition and even cause death. This can be due to the large number of ACE-2 receptors that are occupied by the coronavirus.

How is the relationship between ACE-2 receptors and the clinical condition of children who are milder than adult patients? One hypothesis states that the expression or number of ACE-2 receptors in children is still relatively small compared to adults; this makes the virus unable to adhere optimally to children. This condition could be the reason why children have milder symptoms than adults. However, another hypothesis states that the opposite is true. The ACE-2 receptor in children is high enough or in large numbers but less sensitive to binding to the coronavirus. The protective effect is more dominant than the adverse effect. Also, children often experience other viral infections besides the coronavirus; this will stimulate more antibodies. Some of these hypotheses are the reasons why children's clinical symptoms are milder than those of adults. However, even though children's clinical symptoms are more favorable than adults, children are also carriers that can transmit to adults. Transmission to adults who are nearby will cause fatal conditions for adults, especially those with comorbidities such as Diabetes Mellitus. Therefore, if a child is infected, everyone in contact must be traced, and their status determined.[2,4,5]

The results of laboratory examinations of pediatric patients who have Covid-19 do not provide a typical picture. This is different from adult patients. A study with 1099 patients from 31 provinces in China showed the results of hematology tests, 82.1% of patients had lymphopenia, 36.2% of patients had thrombocytopenia, and 33.7% of patients had leukopenia.[6] The results of laboratory examinations in children with Covid-19 are different from adults; in children with Covid-19, 16.6% had leukopenia, lymphopenia only occurred in 12.9% of patients thrombocytopenia only occurred in 3.2%. patient.[7] The results of laboratory tests of pediatric patients that are not the same as those of adult patients who have confirmed COVID-19 can be explained by the role of the ACE 1 receptor and the ACE 2 receptor in the Renin Angiotensin Aldosterone System (RAA). The Renin-Angiotensin-Aldosterone (RAA) system is closely related to the pathophysiology of COVID-19 infection. In physiological conditions, Angiotensin Converting Enzyme (ACE) is produced in the kidney and the lungs. Angiotensin-Converting Enzyme (ACE) has a function to convert angiotensin I to angiotensin II. Angiotensin II has a vasoconstrictive effect, endothelial activation, and the release of pro-inflammatory cytokines. In the RAA system, normally, angiotensin II will be metabolized by ACE 2. ACE 2 will deactivate angiotensin II to angiotensin 1-7, resulting in vasodilation of blood vessels and anti-inflammatory mediators' release. Covid-19 infection, the SARS-Cov2 virus will bind to the ACE-2 receptor; this will be causing ACE-2's action as a deactivator against angiotensin II, consequently triggering local inflammation, endothelial activation, tissue damage, and increased release of pro-inflammatory cytokines. Angiotensin II activity is increased, and angiotensin 1-7 decreases. In addition to local inflammation, the increased activity of angiotensin II also causes increased platelet activation. In addition, angiotensin II also has a very potent chemotactic effect of recruiting lymphocytes and suppressing lymphocytes. This situation could explain why patients infected with Covid-19 will experience lymphopenia and thrombocytopenia. In COVID-19 patients, angiotensin II levels increased twofold compared to normal conditions. The state of pulmonary vascular inflammation specifically triggers a phenomenon known as ACE-1 shedding, in which ACE-1 bound to the endothelial surface is released into the intestine. As a result of ACE-1 shedding, in the beginning, it will trigger a sharp increase of angiotensin II, which then gradually drops below the physiological level. In addition to decreasing angiotensin II, ACE-1 receptor activity also decreases. The decrease in angiotensin II will trigger an increase in ACE-2 receptor expression. This situation causes vasodilation of blood vessels, capillary leakage, and autoregulation. Patients will be more easily infected with the SARS-Cov2 virus again because of the increased binding of the virus and ACE-2 receptors; besides, the patient will also experience shock due to severe vasodilation. This situation does not fully work in pediatric patients who have a COVID-19 infection. As previously explained, the hypothesis that occurs in pediatric patients is at least the expression of the ACE-2 receptor, or another hypothesis states that the expression of the ACE-2 receptor is increased, but it is less sensitive to binding to the SARS-Cov2 virus.[2,5,8-12] This causes the ACE-2 receptor

to carry out its maximum protective function. In addition, ACE-2 can metabolize angiotensin II so that platelet activation and it is a very potent chemotactic effect to recruit lymphocytes and suppress lymphocytes from angiotensin II do not occur. This could explain why not all pediatric patients infected with Covid-19 will experience lymphopenia and thrombocytopenia. Some flashlights diagnose COVID-19 patients using a scoring system. The scoring system contains clinical aspects, results of hematological examinations, and results of radiological examinations. This system is difficult to implement in pediatric patients because most pediatric patients have mild symptoms, even asymptomatic, and the hematological examination results are not specific. Therefore, the difficulty level of screening pediatric patients is higher than adult patients. In pediatric patients, contact history tracing must also be carried out, because tracing the contact history will enforce the COVID-19 infection.

Other problems for diagnosing pediatric patients who have Covid-19 in Indonesia are the limited number of examination tools, rapid tests, and PCR-RT tests. These problems require the doctors to be very careful in diagnosing Covid-19 in children.

CONFLICT OF INTEREST

No conflict of interest

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